Spark Therapeutics, Inc.
Form 10-K
February 28, 2019
false--12-31FY20182018-12-310001609351YesfalseLarge Accelerated FilerSpark Therapeutics, Inc.falsefalseNoYesONCE0.0010.001150000000371316263776421337111404376863015000000P5Y00050000000400000000
0001609351 2018-01-01 2018-12-31 0001609351 2018-06-30 0001609351 2019-02-15 0001609351 2018-12-31
0001609351 2017-12-31 0001609351 2017-01-01 2017-12-31 0001609351 2016-01-01 2016-12-31 0001609351
once:ContractRevenueMember 2018-01-01 2018-12-31 0001609351 us-gaap:ProductMember 2017-01-01
2017-12-31 0001609351 once:ContractRevenueMember 2017-01-01 2017-12-31 0001609351
us-gaap:ProductMember 2016-01-01 2016-12-31 0001609351 once:ContractRevenueMember 2016-01-01
2016-12-31 0001609351 us-gaap:ProductMember 2018-01-01 2018-12-31 0001609351
us-gaap:AdditionalPaidInCapitalMember 2016-12-31 0001609351 us-gaap:CommonStockMember 2017-01-01
2017-12-31 0001609351 us-gaap:AdditionalPaidInCapitalMember 2017-01-01 2017-12-31 0001609351
us-gaap:AdditionalPaidInCapitalMember 2016-01-01 2016-12-31 0001609351
us-gaap:AccumulatedOtherComprehensiveIncomeMember 2015-12-31 0001609351
us-gaap:TreasuryStockCommonMember 2016-12-31 0001609351 us-gaap:RetainedEarningsMember 2016-01-01
2016-12-31 0001609351 2015-12-31 0001609351 us-gaap:AccumulatedOtherComprehensiveIncomeMember
2017-12-31 0001609351 us-gaap:CommonStockMember 2016-01-01 2016-12-31 0001609351
us-gaap:AccumulatedOtherComprehensiveIncomeMember 2016-01-01 2016-12-31 0001609351
us-gaap:AdditionalPaidInCapitalMember 2017-12-31 0001609351
us-gaap:AccumulatedOtherComprehensiveIncomeMember 2017-01-01 2017-12-31 0001609351 2016-12-31
0001609351 us-gaap:CommonStockMember 2016-12-31 0001609351 us-gaap:RetainedEarningsMember 2017-12-31
0001609351 us-gaap:TreasuryStockCommonMember 2015-12-31 0001609351
us-gaap:TreasuryStockCommonMember 2017-01-01 2017-12-31 0001609351 us-gaap:CommonStockMember
2015-12-31 0001609351 us-gaap:AccumulatedOtherComprehensiveIncomeMember 2016-12-31 0001609351
us-gaap:TreasuryStockCommonMember 2017-12-31 0001609351 us-gaap:CommonStockMember 2017-12-31
0001609351 us-gaap:RetainedEarningsMember 2016-12-31 0001609351 us-gaap:RetainedEarningsMember
2017-01-01 2017-12-31 0001609351 us-gaap:RetainedEarningsMember 2015-12-31 0001609351
us-gaap:AdditionalPaidInCapitalMember 2015-12-31 0001609351 us-gaap:CommonStockMember 2018-01-01
2018-12-31 0001609351 us-gaap:TreasuryStockCommonMember 2018-12-31 0001609351
us-gaap:RetainedEarningsMember 2018-12-31 0001609351 us-gaap:RetainedEarningsMember 2018-01-01
2018-12-31 0001609351 us-gaap:AdditionalPaidInCapitalMember 2018-01-01 2018-12-31 0001609351
us-gaap:AccumulatedOtherComprehensiveIncomeMember 2018-12-31 0001609351 us-gaap:CommonStockMember
2018-12-31 0001609351 us-gaap:AccumulatedOtherComprehensiveIncomeMember 2018-01-01 2018-12-31
0001609351 us-gaap:TreasuryStockCommonMember 2018-01-01 2018-12-31 0001609351
us-gaap:AdditionalPaidInCapitalMember 2018-12-31 0001609351 us-gaap:RetainedEarningsMember 2018-01-01
0001609351 2018-01-01 0001609351 us-gaap:AccumulatedOtherComprehensiveIncomeMember 2018-01-01
0001609351 us-gaap:AccumulatedTranslationAdjustmentMember 2018-01-01 0001609351
us-gaap:AccumulatedNetUnrealizedInvestmentGainLossMember 2018-01-01 0001609351
us-gaap:AccumulatedTranslationAdjustmentMember 2018-01-01 2018-12-31 0001609351
us-gaap:AccumulatedTranslationAdjustmentMember 2018-12-31 0001609351
us-gaap:AccumulatedGainLossNetCashFlowHedgeParentMember 2018-12-31 0001609351
us-gaap:AccumulatedGainLossNetCashFlowHedgeParentMember 2017-12-31 0001609351
us-gaap:AccumulatedGainLossNetCashFlowHedgeParentMember 2018-01-01 2018-12-31 0001609351
us-gaap:AccumulatedNetUnrealizedInvestmentGainLossMember 2018-01-01 2018-12-31 0001609351
us-gaap:AccumulatedNetUnrealizedInvestmentGainLossMember 2017-12-31 0001609351
us-gaap:AccumulatedNetUnrealizedInvestmentGainLossMember 2018-12-31 0001609351
us-gaap:AccumulatedGainLossNetCashFlowHedgeParentMember 2018-01-01 0001609351
us-gaap:AccumulatedTranslationAdjustmentMember 2017-12-31 0001609351
once:UnvestedRestrictedCommonSharesMember 2017-01-01 2017-12-31 0001609351
us-gaap:EmployeeStockOptionMember 2016-01-01 2016-12-31 0001609351

once:UnvestedRestrictedCommonSharesMember 2018-01-01 2018-12-31 0001609351
us-gaap:EmployeeStockOptionMember 2018-01-01 2018-12-31 0001609351 us-gaap:EmployeeStockOptionMember
2017-01-01 2017-12-31 0001609351 once:UnvestedRestrictedCommonSharesMember 2016-01-01 2016-12-31
0001609351 srt:MaximumMember us-gaap:AccountingStandardsUpdate201602Member
us-gaap:ScenarioForecastMember us-gaap:SubsequentEventMember 2019-01-01 0001609351 2013-03-13
2018-12-31 0001609351 us-gaap:ComputerEquipmentMember 2018-01-01 2018-12-31 0001609351
us-gaap:FurnitureAndFixturesMember 2018-01-01 2018-12-31 0001609351
once:LaboratoryAndOfficeEquipmentMember 2018-01-01 2018-12-31 0001609351 srt:MinimumMember
us-gaap:AccountingStandardsUpdate201602Member us-gaap:ScenarioForecastMember
us-gaap:SubsequentEventMember 2019-01-01 0001609351 us-gaap:AccountingStandardsUpdate201601Member
us-gaap:AccumulatedOtherComprehensiveIncomeMember 2018-01-01 0001609351
us-gaap:AccountingStandardsUpdate201601Member us-gaap:RetainedEarningsMember 2018-01-01 0001609351
us-gaap:SoftwareAndSoftwareDevelopmentCostsMember 2018-01-01 2018-12-31 0001609351
us-gaap:CorporateDebtSecuritiesMember 2017-12-31 0001609351
us-gaap:USGovernmentAgenciesDebtSecuritiesMember 2018-12-31 0001609351
us-gaap:CorporateDebtSecuritiesMember 2018-12-31 0001609351
us-gaap:USGovernmentAgenciesDebtSecuritiesMember 2017-12-31 0001609351
us-gaap:USGovernmentAgenciesDebtSecuritiesMember us-gaap:FairValueInputsLevel3Member
us-gaap:FairValueMeasurementsRecurringMember 2018-12-31 0001609351 us-gaap:CertificatesOfDepositMember
us-gaap:FairValueInputsLevel3Member us-gaap:FairValueMeasurementsRecurringMember 2018-12-31 0001609351
us-gaap:MoneyMarketFundsMember us-gaap:FairValueInputsLevel2Member
us-gaap:FairValueMeasurementsRecurringMember 2017-12-31 0001609351
us-gaap:CorporateDebtSecuritiesMember us-gaap:FairValueInputsLevel2Member
us-gaap:FairValueMeasurementsRecurringMember 2017-12-31 0001609351 us-gaap:MoneyMarketFundsMember
us-gaap:FairValueInputsLevel1Member us-gaap:FairValueMeasurementsRecurringMember 2017-12-31 0001609351
us-gaap:USGovernmentAgenciesDebtSecuritiesMember us-gaap:FairValueInputsLevel2Member
us-gaap:FairValueMeasurementsRecurringMember 2017-12-31 0001609351
us-gaap:USGovernmentAgenciesDebtSecuritiesMember us-gaap:FairValueInputsLevel1Member
us-gaap:FairValueMeasurementsRecurringMember 2018-12-31 0001609351
us-gaap:CorporateDebtSecuritiesMember us-gaap:FairValueInputsLevel2Member
us-gaap:FairValueMeasurementsRecurringMember 2018-12-31 0001609351 us-gaap:CertificatesOfDepositMember
us-gaap:FairValueInputsLevel2Member us-gaap:FairValueMeasurementsRecurringMember 2018-12-31 0001609351
us-gaap:CorporateDebtSecuritiesMember us-gaap:FairValueInputsLevel3Member
us-gaap:FairValueMeasurementsRecurringMember 2017-12-31 0001609351
us-gaap:USGovernmentAgenciesDebtSecuritiesMember us-gaap:FairValueInputsLevel2Member
us-gaap:FairValueMeasurementsRecurringMember 2018-12-31 0001609351 us-gaap:MoneyMarketFundsMember
us-gaap:FairValueInputsLevel3Member us-gaap:FairValueMeasurementsRecurringMember 2017-12-31 0001609351
us-gaap:MoneyMarketFundsMember us-gaap:FairValueInputsLevel1Member
us-gaap:FairValueMeasurementsRecurringMember 2018-12-31 0001609351
us-gaap:CorporateDebtSecuritiesMember us-gaap:FairValueInputsLevel3Member
us-gaap:FairValueMeasurementsRecurringMember 2018-12-31 0001609351 us-gaap:MoneyMarketFundsMember
us-gaap:FairValueInputsLevel3Member us-gaap:FairValueMeasurementsRecurringMember 2018-12-31 0001609351
us-gaap:CorporateDebtSecuritiesMember us-gaap:FairValueInputsLevel1Member
us-gaap:FairValueMeasurementsRecurringMember 2017-12-31 0001609351 us-gaap:CertificatesOfDepositMember
us-gaap:FairValueInputsLevel1Member us-gaap:FairValueMeasurementsRecurringMember 2018-12-31 0001609351
us-gaap:USGovernmentAgenciesDebtSecuritiesMember us-gaap:FairValueInputsLevel1Member
us-gaap:FairValueMeasurementsRecurringMember 2017-12-31 0001609351
us-gaap:USGovernmentAgenciesDebtSecuritiesMember us-gaap:FairValueInputsLevel3Member
us-gaap:FairValueMeasurementsRecurringMember 2017-12-31 0001609351 us-gaap:MoneyMarketFundsMember
us-gaap:FairValueInputsLevel2Member us-gaap:FairValueMeasurementsRecurringMember 2018-12-31 0001609351
us-gaap:CorporateDebtSecuritiesMember us-gaap:FairValueInputsLevel1Member

us-gaap:FairValueMeasurementsRecurringMember 2018-12-31 0001609351 2018-05-01 2018-05-31 0001609351 once:GenableMember 2016-03-07 0001609351 once:GenableMember 2016-03-07 2016-03-07 0001609351 once:GenableMember once:GenableMember 2016-03-07 0001609351 once:GenableMember us-gaap:InProcessResearchAndDevelopmentMember 2016-03-07 0001609351 us-gaap:CommonStockMember once:GenableMember 2016-03-07 2016-03-07 0001609351 us-gaap:LeaseholdImprovementsMember 2018-12-31 0001609351 once:ComputerandSoftwareMember 2018-12-31 0001609351 once:LaboratoryEquipmentMember 2018-12-31 0001609351 us-gaap:LeaseholdImprovementsMember 2017-12-31 0001609351 us-gaap:FurnitureAndFixturesMember 2018-12-31 0001609351 us-gaap:AssetUnderConstructionMember 2018-12-31 0001609351 once:OneDrexelPlazaResearchFacilityMember once:BuiltToSuitLeaseMember 2017-12-31 0001609351 us-gaap:AssetUnderConstructionMember 2017-12-31 0001609351 once:ComputerandSoftwareMember 2017-12-31 0001609351 once:OneDrexelPlazaResearchFacilityMember once:BuiltToSuitLeaseMember 2018-12-31 0001609351 us-gaap:FurnitureAndFixturesMember 2017-12-31 0001609351 once:LaboratoryEquipmentMember 2017-12-31 0001609351 us-gaap:OfficeEquipmentMember 2017-12-31 0001609351 us-gaap:OfficeEquipmentMember 2018-12-31 0001609351 once:MachineryAndEquipmentAndOtherAssetsPurchasedLoanMember us-gaap:SecuredDebtMember 2018-12-31 0001609351 once:MachineryAndEquipmentAndOtherAssetsPurchasedLoanMember us-gaap:SecuredDebtMember 2017-12-31 0001609351 once:TermLoanCreditAgreementMember us-gaap:SecuredDebtMember 2018-12-31 0001609351 once:TermLoanCreditAgreementMember us-gaap:SecuredDebtMember 2017-12-31 0001609351 once:TermLoanCreditAgreementMember us-gaap:SecuredDebtMember us-gaap:LondonInterbankOfferedRateLIBORMember 2018-07-03 2018-07-03 0001609351 once:MachineryAndEquipmentAndOtherAssetsPurchasedLoanMember us-gaap:SecuredDebtMember 2018-01-01 2018-12-31 0001609351 us-gaap:OtherCurrentLiabilitiesMember us-gaap:InterestRateSwapMember us-gaap:DesignatedAsHedgingInstrumentMember 2018-12-31 0001609351 once:TermLoanCreditAgreementMember us-gaap:InterestRateSwapMember 2018-07-03 0001609351 once:TermLoanCreditAgreementMember us-gaap:SecuredDebtMember 2018-07-03 0001609351 once:MachineryAndEquipmentAndOtherAssetsPurchasedLoanMember us-gaap:SecuredDebtMember 2017-01-01 2017-12-31 0001609351 once:MachineryAndEquipmentAndOtherAssetsPurchasedLoanMember us-gaap:SecuredDebtMember 2016-01-01 2016-12-31 0001609351 once:MachineryAndEquipmentAndOtherAssetsPurchasedLoanMember us-gaap:SecuredDebtMember 2016-08-01 2016-08-31 0001609351 once:MachineryAndEquipmentAndOtherAssetsPurchasedLoanMember us-gaap:SecuredDebtMember 2016-08-31 0001609351 once:TermLoanCreditAgreementMember us-gaap:SecuredDebtMember 2018-01-01 2018-12-31 0001609351 us-gaap:OtherNoncurrentLiabilitiesMember us-gaap:InterestRateSwapMember us-gaap:DesignatedAsHedgingInstrumentMember 2018-12-31 0001609351 us-gaap:InterestRateSwapMember us-gaap:CashFlowHedgingMember us-gaap:DesignatedAsHedgingInstrumentMember 2018-01-01 2018-12-31 0001609351 us-gaap:InterestRateSwapMember us-gaap:DesignatedAsHedgingInstrumentMember 2018-12-31 0001609351 us-gaap:InterestRateSwapMember us-gaap:DesignatedAsHedgingInstrumentMember 2018-07-03 0001609351 us-gaap:CommonStockMember once:PublicStockOfferingMember 2017-08-09 2017-08-09 0001609351 us-gaap:RestrictedStockMember us-gaap:GeneralAndAdministrativeExpenseMember 2016-01-01 2016-12-31 0001609351 us-gaap:CommonStockMember once:PublicStockOfferingMember 2016-06-20 0001609351 us-gaap:RestrictedStockMember us-gaap:GeneralAndAdministrativeExpenseMember 2017-01-01 2017-12-31 0001609351 us-gaap:CommonStockMember once:PublicStockOfferingMember 2016-06-20 2016-06-20 0001609351 us-gaap:RestrictedStockMember us-gaap:ResearchAndDevelopmentExpenseMember 2017-01-01 2017-12-31 0001609351 us-gaap:CommonStockMember us-gaap:ShareBasedCompensationAwardTrancheOneMember 2018-01-01 2018-12-31 0001609351 us-gaap:CommonStockMember us-gaap:ShareBasedCompensationAwardTrancheTwoMember 2018-01-01 2018-12-31 0001609351 us-gaap:CommonStockMember once:PublicStockOfferingMember 2017-08-09 0001609351 once:UniversityofPennsylvaniaMember once:LicenseAgreementMember 2015-01-01 2018-12-31 0001609351 once:UniversityofPennsylvaniaMember once:LicenseAgreementMember 2014-01-01 2014-12-31 0001609351 us-gaap:RestrictedStockMember us-gaap:ResearchAndDevelopmentExpenseMember 2018-01-01 2018-12-31 0001609351 us-gaap:RestrictedStockMember us-gaap:ResearchAndDevelopmentExpenseMember 2016-01-01

2016-12-31 0001609351 us-gaap:RestrictedStockMember 2017-12-31 0001609351 us-gaap:RestrictedStockMember 2016-12-31 0001609351 us-gaap:RestrictedStockMember 2017-01-01 2017-12-31 0001609351 us-gaap:RestrictedStockMember 2018-01-01 2018-12-31 0001609351 us-gaap:RestrictedStockMember 2018-12-31 0001609351 us-gaap:EmployeeStockOptionMember 2018-01-01 2018-12-31 0001609351 us-gaap:GeneralAndAdministrativeExpenseMember 2016-01-01 2016-12-31 0001609351 us-gaap:PerformanceSharesMember 2018-12-31 0001609351 us-gaap:EmployeeStockOptionMember 2018-12-31 0001609351 us-gaap:EmployeeStockMember 2018-12-31 0001609351 us-gaap:EmployeeStockMember once:TwoThousandFifteenEmployeeStockPurchasePlanMember 2018-12-31 0001609351 us-gaap:ResearchAndDevelopmentExpenseMember 2017-01-01 2017-12-31 0001609351 us-gaap:EmployeeStockMember 2017-01-01 2017-12-31 0001609351 once:TwoThousandFifteenStockIncentivePlanMember 2018-12-31 0001609351 us-gaap:ResearchAndDevelopmentExpenseMember 2018-01-01 2018-12-31 0001609351 us-gaap:EmployeeStockMember 2018-01-01 2018-12-31 0001609351 us-gaap:EmployeeStockOptionMember 2017-01-01 2017-12-31 0001609351 us-gaap:EmployeeStockMember once:TwoThousandFifteenEmployeeStockPurchasePlanMember 2018-01-01 2018-01-31 0001609351 us-gaap:GeneralAndAdministrativeExpenseMember 2017-01-01 2017-12-31 0001609351 us-gaap:PerformanceSharesMember 2018-01-01 2018-12-31 0001609351 us-gaap:ResearchAndDevelopmentExpenseMember 2016-01-01 2016-12-31 0001609351 us-gaap:GeneralAndAdministrativeExpenseMember 2018-01-01 2018-12-31 0001609351 once:TwoThousandFifteenStockIncentivePlanMember 2018-01-01 2018-01-31 0001609351 us-gaap:EmployeeStockOptionMember 2016-01-01 2016-12-31 0001609351 us-gaap:PerformanceSharesMember 2017-12-31 0001609351 us-gaap:PerformanceSharesMember 2017-01-01 2017-12-31 0001609351 us-gaap:PerformanceSharesMember 2016-12-31 0001609351 us-gaap:PerformanceSharesMember 2016-01-01 2016-12-31 0001609351 us-gaap:EmployeeStockMember 2016-01-01 2016-12-31 0001609351 once:OneDrexelPlazaResearchFacilityMember 2017-11-20 0001609351 once:LeaseofOfficeSpaceMember 2018-12-31 0001609351 once:OneDrexelPlazaResearchFacilityMember 2017-12-31 0001609351 once:CorporateHeadquartersinPhiladelphiaMember once:LeaseofOfficeSpaceMember 2016-02-29 0001609351 once:LeaseofLaboratoryandOfficeSpaceMember 2014-01-01 2014-12-31 0001609351 once:UniversityofPennsylvaniaMember srt:MaximumMember once:MilestonePaymentsMember once:LicenseAgreementMember 2014-12-31 0001609351 once:CorporateHeadquartersinPhiladelphiaMember once:LeaseofOfficeSpaceMember 2017-11-30 0001609351 once:CorporateHeadquartersinPhiladelphiaMember once:LeaseofOfficeSpaceMember 2016-11-30 0001609351 once:BrammerBioAgreementMember 2018-08-01 2018-08-31 0001609351 once:CorporateHeadquartersinPhiladelphiaMember once:SubleaseofOfficeSpaceMember 2015-11-30 0001609351 once:PhiladelphiaPropertyMember once:LeaseofOfficeSpaceMember 2018-01-01 2018-12-31 0001609351 once:UniversityofPennsylvaniaMember once:LicenseAgreementMember 2014-12-01 2014-12-31 0001609351 once:OneDrexelPlazaResearchFacilityMember 2018-01-01 2018-12-31 0001609351 once:LeaseofOfficeSpaceMember 2017-11-01 2017-11-30 0001609351 once:CorporateHeadquartersinPhiladelphiaMember once:SubleaseofOfficeSpaceMember 2016-11-01 2016-11-30 0001609351 once:CorporateHeadquartersinPhiladelphiaMember once:LeaseofOfficeSpaceMember 2017-01-31 0001609351 once:PhiladelphiaPropertyMember once:LeaseofOfficeSpaceMember 2018-05-31 0001609351 once:LeaseofOfficeSpaceMember 2017-12-31 0001609351 once:LeaseofOfficeSpaceMember 2018-01-01 2018-12-31 0001609351 once:MasterResearchServicesAgreementMember once:ChildrenHospitalOfPhiladelphiaMember 2016-01-01 2016-12-31 0001609351 once:ChildrenHospitalOfPhiladelphiaMember 2018-12-31 0001609351 once:MasterResearchServicesAgreementMember once:ChildrenHospitalOfPhiladelphiaMember 2017-01-01 2017-12-31 0001609351 once:ChildrenHospitalOfPhiladelphiaMember 2017-12-31 0001609351 once:MasterResearchServicesAgreementMember once:ChildrenHospitalOfPhiladelphiaMember 2018-01-01 2018-12-31 0001609351 once:TechnologyAndLicenseAgreementMember once:ChildrenHospitalOfPhiladelphiaMember 2016-01-01 2016-12-31 0001609351 once:TechnologyAndLicenseAgreementMember once:ChildrenHospitalOfPhiladelphiaMember 2018-01-01 2018-12-31 0001609351 once:TechnologyAndLicenseAgreementMember

once:ChildrenHospitalOfPhiladelphiaMember 2017-01-01 2017-12-31 0001609351
once:NovartisLicensingAndCommercializationAgreementMember 2018-10-01 2018-12-31 0001609351
once:NovartisLicensingAndCommercializationAgreementMember 2018-12-31 0001609351
once:SelectaLicenseAgreementMember 2017-10-01 2017-10-31 0001609351 us-gaap:LicensingAgreementsMember
once:SelectaLicenseAgreementMember 2016-12-01 2016-12-31 0001609351 srt:MaximumMember
once:SelectaLicenseAgreementMember 2016-12-01 2016-12-31 0001609351 once:CommercialMilestoneMember
2016-12-01 2016-12-31 0001609351 once:SelectaLicenseAgreementMember 2017-06-01 2017-06-30 0001609351
once:PfizerCollaborationAndLicenseAgreementMember 2017-11-01 2017-11-30 0001609351
once:PfizerCollaborationAndLicenseAgreementMember 2014-01-01 2014-12-31 0001609351
once:SelectaLicenseAgreementMember 2016-12-01 2016-12-31 0001609351
once:PfizerCollaborationAndLicenseAgreementMember 2017-01-01 2017-12-31 0001609351
once:SelectaLicenseAgreementMember 2017-10-31 0001609351
once:PfizerCollaborationAndLicenseAgreementMember 2018-02-01 2018-02-28 0001609351 srt:MinimumMember
once:SelectaLicenseAgreementMember 2016-12-01 2016-12-31 0001609351
us-gaap:ResearchAndDevelopmentExpenseMember once:PfizerCollaborationAndLicenseAgreementMember
2016-01-01 2016-12-31 0001609351 once:PfizerCollaborationAndLicenseAgreementMember 2017-11-30
0001609351 us-gaap:LicensingAgreementsMember once:SelectaLicenseAgreementMember 2017-06-01 2017-06-30
0001609351 once:NovartisLicensingAndCommercializationAgreementMember 2018-01-01 2018-03-31 0001609351
once:PfizerCollaborationAndLicenseAgreementMember 2018-01-01 2018-12-31 0001609351
us-gaap:CommonStockMember once:SelectaLicenseAgreementMember 2016-12-01 2016-12-31 0001609351
once:ContractRevenueMember once:PfizerCollaborationAndLicenseAgreementMember 2018-01-01 2018-12-31
0001609351 us-gaap:CommonStockMember once:SelectaLicenseAgreementMember 2017-06-01 2017-06-30
0001609351 once:SelectaLicenseAgreementMember 2016-12-31 0001609351
once:PfizerCollaborationAndLicenseAgreementMember 2016-01-01 2016-12-31 0001609351
once:PfizerCollaborationAndLicenseAgreementMember 2018-07-01 2018-07-31 0001609351
once:AdditionalProductCandidatesMember 2018-01-01 2018-12-31 0001609351
once:PfizerCollaborationAndLicenseAgreementMember 2018-02-01 2018-12-31 0001609351
once:NovartisLicensingAndCommercializationAgreementMember 2018-01-01 2018-12-31 0001609351
us-gaap:ResearchAndDevelopmentExpenseMember once:PfizerCollaborationAndLicenseAgreementMember
2017-01-01 2017-12-31 0001609351 us-gaap:CommonStockMember once:SelectaLicenseAgreementMember
2017-10-01 2017-10-31 0001609351 once:PfizerCollaborationAndLicenseAgreementMember 2014-12-01
2014-12-31 0001609351 us-gaap:ResearchAndDevelopmentExpenseMember
once:PfizerCollaborationAndLicenseAgreementMember 2018-01-01 2018-12-31 0001609351
once:SelectaLicenseAgreementMember 2017-06-01 2017-10-31 0001609351
once:DevelopmentandRegulatoryMilestoneMember 2016-12-01 2016-12-31 0001609351
once:SelectaLicenseAgreementMember 2017-06-30 0001609351 us-gaap:LicensingAgreementsMember
once:SelectaLicenseAgreementMember 2017-10-01 2017-10-31 0001609351 us-gaap:DomesticCountryMember
once:OrphanDrugandResearchTaxCreditCarryforwardMember 2018-12-31 0001609351
us-gaap:StateAndLocalJurisdictionMember 2018-12-31 0001609351 us-gaap:DomesticCountryMember 2018-12-31
0001609351 us-gaap:DomesticCountryMember us-gaap:TaxYear2017Member 2018-12-31 0001609351
us-gaap:ForeignCountryMember 2018-12-31 0001609351 us-gaap:DomesticCountryMember
us-gaap:ResearchMember 2018-12-31 0001609351 2018-04-01 2018-06-30 0001609351 2018-10-01 2018-12-31
0001609351 2018-01-01 2018-03-31 0001609351 2018-07-01 2018-09-30 0001609351 2017-10-01 2017-12-31
0001609351 2017-04-01 2017-06-30 0001609351 2017-01-01 2017-03-31 0001609351 2017-07-01 2017-09-30
0001609351 once:RocheHoldingsInc.Member us-gaap:SubsequentEventMember 2019-02-22 iso4217:USD
xbrli:shares once:segment xbrli:pure once:distribution_model once:reporting_unit iso4217:USD xbrli:shares utreg:sqft
once:target

Table of Contents

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, DC 20549

FORM 10-K

(Mark One)

x **ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the fiscal year ended December 31, 2018

OR

o **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the transition period from _____ to _____

Commission File Number: 001-36819

Spark Therapeutics, Inc.
(Exact Name of Registrant as Specified in Its Charter)

Delaware	**46-2654405**
(State or Other Jurisdiction of Incorporation or Organization)	**(IRS Employer Identification No.)**
3737 Market Street Suite 1300 Philadelphia, PA	**19104**
(Address of Principal Executive Offices)	**(Zip Code)**

(888) 772-7560
(Registrant's Telephone Number, Including Area Code)
Securities registered pursuant to Section 12(b) of the Act:

Title of each class	**Name of each exchange on which registered**
Common Stock, $0.001 par value per share	**Nasdaq Global Select Market**

Securities registered pursuant to Section 12(g) of the Act: None

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes x No ¨

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or 15(d) of the Act. Yes ¨ No x

Indicate by check mark whether the registrant: (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes x No ¨

Table of Contents

Indicate by check mark whether the registrant has submitted electronically every Interactive Data File required to be submitted pursuant to Rule 405 of Regulation S-T during the preceding 12 months (or for such shorter period that the registrant was required to submit such files). Yes x No ¨

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (§ 229.405 of this chapter) is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. ¨

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, a smaller reporting company, or an emerging growth company. See the definitions of "large accelerated filer", "accelerated filer", "smaller reporting company", and "emerging growth company" in Rule 12b-2 of the Exchange Act.

Large accelerated filer	x	Accelerated filer	¨
Non-accelerated filer	¨	Smaller reporting company	¨
		Emerging growth company	¨

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ¨

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act). Yes ¨ No x

As of June 30, 2018, the last day of the registrant's most recently completed second fiscal quarter, the aggregate market value of the common stock held by non-affiliates of the registrant was approximately $2,583,300,000, based upon the closing price of the registrant's common stock on June 30, 2018.

As of February 15, 2019, there were 37,961,302 shares of the registrant's common stock, par value $0.001 per share, outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

The registrant intends to file a definitive proxy statement pursuant to Regulation 14A in connection with its 2019 Annual Meeting of Stockholders. Portions of such proxy statement are incorporated by reference into Part III of this Annual Report on Form 10-K.

Table of Contents

TABLE OF CONTENTS

Table of Contents

Forward-looking statements

This Annual Report on Form 10-K contains forward-looking statements that involve substantial risks and uncertainties. All statements, other than statements of historical facts, contained in this Annual Report on Form 10-K, including statements regarding our future results of operations and financial position, business strategy and plans and objectives of management for future operations, are forward-looking statements. The words “may,” “will,” “should,” “expects,” “plans,” “anticipates,” “could,” “intends,” “target,” “projects,” “contemplates,” “believes,” “estimates,” “predicts,” “continue” or the negative of these terms or other similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words.

The forward-looking statements in this Annual Report on Form 10-K include, among other things, statements about:

- the occurrence of any event, change or other circumstance that could give rise to the termination of the merger agreement that we entered into with Roche Holdings, Inc., or Roche, and its wholly owned acquisition subsidiary on February 22, 2019, pursuant to which we expect to become a wholly owned subsidiary of Roche;
- the failure to satisfy required closing conditions under the merger agreement, including, but not limited to, the tender of a minimum number of our outstanding shares of common stock in the related tender offer and the receipt of required regulatory approvals, or the failure to complete the merger in a timely manner;
- risks related to disruption of management’s attention from our ongoing business operations due to the pendency of the transaction with Roche;
- the effect of the announcement of the transaction with Roche on our operating results and business generally, including, but not limited to, our ability to retain and hire key personnel and maintain our relationships with customers, strategic partners, suppliers, regulatory authorities and others with whom we do business;
- the impact of the pending transaction with Roche on our strategic plans and operations and our ability to respond effectively to competitive pressures, industry developments and future opportunities;
- the outcome of any legal proceedings that may be instituted against us and others relating to the merger agreement;
- our expectations regarding our commercial launch of LUXTURNA® (voretigene neparvovec-rzyl) and our plans to develop and commercialize our other product candidates;
- our estimates regarding the potential market opportunity for LUXTURNA and our product candidates;
- our ability to maintain our current, and enter into additional, agreements involving outcomes-based rebates and innovative contracting models with payers for LUXTURNA or any future products;
- the timing, progress and results of clinical trials for *SPK-7001*, *SPK-9001*, *SPK-8011, SPK-8016* and our other product candidates, including statements regarding the timing of initiation and completion of clinical trials, dosing of subjects and the period during which the results of the trials will become available;
- the initiation, timing, progress and results of future preclinical studies and clinical trials, and our research and development programs for our other product candidates;
- our ability to achieve milestones and receive payments under our collaborations;
- our commercialization, medical affairs, marketing and manufacturing capabilities and strategy;
- the implementation of our business model, strategic plans for our business, product candidates and technology;
- the scalability and commercial viability of our proprietary manufacturing processes;
- our expectations about the rate and degree of market acceptance and clinical utility of LUXTURNA and our product candidates, in particular, and gene therapy in general;
- our competitive position;
- our intellectual property position;
- developments and projections relating to our competitors and our industry;
- our ability to maintain and establish collaborations or obtain additional funding;
- our expectations related to the use of our capital resources;
- our estimates regarding expenses, future revenue, capital requirements and needs for additional financing; and
- the impact of government laws and regulations.

Table of Contents

We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make. We have included important factors in the cautionary statements included in this Annual Report on Form 10-K, particularly in the "Risk Factors" section, that could cause actual results or events to differ materially from the forward-looking statements that we make. Our forward-looking statements do not reflect the potential impact of any future acquisitions, mergers, dispositions, joint ventures or investments we may make and do not assume the consummation of our proposed transaction with Roche unless specifically stated otherwise.

You should read this Annual Report on Form 10-K and the documents that we have filed as exhibits to this Annual Report on Form 10-K completely and with the understanding that our actual future results may be materially different from what we expect. We do not assume any obligation to update any forward-looking statements, whether as a result of new information, future events or otherwise, except as required by applicable law.

Table of Contents

PART I.

Item 1. Business

On February 22, 2019, we entered into a definitive merger agreement to be acquired by Roche Holdings, Inc., or Roche. Pursuant to the merger agreement, and upon the terms and subject to the conditions thereof, a wholly owned acquisition subsidiary of Roche, or Merger Sub, will commence a cash tender offer, or the tender offer, to acquire all of the issued and outstanding shares of our common stock at a price per share of $114.50, net to the seller of such shares in cash, without interest, subject to any withholding of taxes required by applicable law. The completion of the tender offer will be conditioned on at least a majority of the shares of our outstanding common stock having been validly tendered into and not withdrawn from the offer, receipt of certain regulatory approvals, and other customary conditions.

Following the completion of the tender offer, Merger Sub will merge with and into our company, with our company surviving as a wholly owned subsidiary of Roche. The merger will be governed by Section 251(h) of the General Corporation Law of the State of Delaware, with no stockholder vote required to consummate the merger. In the merger, each outstanding share of our common stock (other than shares of common stock held by us as treasury stock, or owned by Roche or Merger Sub or held by stockholders who are entitled to demand, and who properly demand, appraisal rights under Delaware law) will be converted into the right to receive $114.50 per share in cash, without interest, subject to any withholding of taxes required by applicable law.

We expect the transaction to close in the second quarter of 2019. If the transaction is completed, it is expected that our common stock will be removed from listing on the NASDAQ Stock Market and from registration under Section 12(b) of the Securities Exchange Act of 1934, as amended.

See Part I, Item 1A, “Risk Factors,” Part II, Item 7, “Management's Discussion and Analysis of Financial Condition and Results of Operations,” and Note 19 of the Notes to Consolidated Financial Statements included in this report for additional information regarding the transaction.

Overview

We are a leader in the field of gene therapy, seeking to transform the lives of patients suffering from debilitating genetic diseases by developing potentially one-time, life-altering treatments. The goal of gene therapy is to overcome the effects of a malfunctioning, disease-causing gene. Gene therapies have the potential to provide long-lasting effects, dramatically and positively changing the lives of patients with conditions where no, or only palliative, therapies exist. We have built a pipeline of gene therapy product candidates that are directed to the retina, the liver and the central nervous system.

In December 2017, the U.S. Food and Drug Administration, or FDA, approved LUXTURNA™ (voretigene neparvovec-rzyl) for the treatment of patients with viable retinal cells and confirmed biallelic *RPE65* mutation-associated retinal dystrophy, a genetic blinding condition caused by mutations in the *RPE65* gene. LUXTURNA is the first FDA-approved gene therapy for a genetic disease, the first and only pharmacological treatment for an inherited retinal disease, or IRD, and the first adeno-associated virus, or AAV, vector gene therapy approved in the United States. LUXTURNA is manufactured at our manufacturing facility located in Philadelphia, which is the first licensed manufacturing facility in the United States for a gene therapy treating an inherited disease. LUXTURNA has received orphan drug status. In January 2018, we entered into a license and commercialization agreement with Novartis Pharma AG, or Novartis, for the development and commercialization of voretigene neparvovec outside the United States. In November 2018, we received approval from the European Medicines Agency, or EMA, for the marketing authorization of LUXTURNA in all 28 member states of the European Union, as well as Iceland, Liechtenstein and Norway.

We are supporting the appropriate use of LUXTURNA in the United States through small, targeted commercial and medical affairs teams. LUXTURNA is administered by trained retinal surgeons at selected treatment centers in the United States that specialize in treating IRDs. In January 2018, we announced two novel payer programs to help ensure eligible patients in the United States have access to LUXTURNA: (i) an innovative contracting model that includes an option for direct-to-payer contracting; and (ii) an outcomes-based rebate arrangement with a short-term efficacy measure and a long-term durability measure.

We have three gene therapy product candidates, to which we retain global commercialization rights, in clinical development: (i) *SPK-8011*, our lead product candidate in the *SPK-FVIII* program for hemophilia A; (ii) *SPK-8016*, a product candidate for the hemophilia A inhibitor market; and (iii) *SPK-7001*, targeting choroideremia, or CHM. A fourth clinical-stage product candidate, *SPK-9001,* our lead product candidate in the *SPK-FIX* program for hemophilia B, recently was transitioned

Table of Contents

to Pfizer Inc., or Pfizer, pursuant to our license agreement with Pfizer. In July 2018, Pfizer announced the initiation of a Phase 3 program for *SPK-9001*, now referred to as PF-06838435 or fidanacogene elaparvovec.

In our *SPK-FVIII* program for the treatment of hemophilia A, we initiated a dose-escalating Phase 1/2 clinical trial for our lead product candidate, *SPK-8011*, in 2017. As of a November 2, 2018, data cutoff date, we had enrolled 12 participants in the trial: two at a dose of 5 x 10^{11} vector genomes (vg)/kilogram (kg) of body weight, three at a dose of 1 x 10^{12} vg/kg and seven at a dose of 2 x 10^{12} vg/kg. Across all 12 participants at the three doses tested, we saw a 94% reduction in bleeding and a 95% reduction in infusions. In the 2 x 10^{12} vg/kg dose cohort, five of the seven participants had reduced their overall bleeds and infusions by 100% and 99% , respectively (calculated based on data after week four). We also saw evidence of stable, durable factor VIII activity levels in all participants that have been followed for greater than one year. We demonstrated a dose response, with higher doses, on average, leading to higher factor VIII levels. No participant developed factor VIII inhibitors, no thromboembolic events have been reported and transaminase elevations were infrequent and transient. One participant was electively admitted to the hospital to receive intravenous administration of methylprednisolone rather than having the infusions on an outpatient basis. The admission met the criteria for a serious adverse event, or SAEs. We plan to incorporate a course of prophlactic steriods going forward in the development program.

We have scaled our mammalian cell-based suspension process to a 400 liter process and have achieved initial yields that are supportive of our future clinical and commercial requirements. Analytical and non-clinical testing demonstrated comparability of material manufactured with this suspension process to material manufactured with our adherent process. We have secured dedicated manufacturing capacity at Brammer Bio MA LLC's, or Brammer Bio's, facility in Cambridge, Massachusetts.

We recently initiated a Phase 3 clinical program for *SPK-8011*, beginning with a run-in study. In February 2018, FDA granted *SPK-8011* breakthrough therapy designation. We retain global commercialization rights to the *SPK-FVIII* program.

We have additional product candidates in the *SPK-FVIII* program that are intended to target specific sub-populations of hemophilia A patients, the first of which will target the hemophilia A inhibitor market using a novel, internally developed product candidate, *SPK-8016*. Our Investigational New Drug, or IND, for *SPK-8016* has been cleared and, per agreement with FDA, we initiated dosing in this Phase 1/2 study in a cohort similar to the patient cohort in our on-going *SPK-8011* Phase 1/2 study in order to establish safety before expanding into participants representing segments of the inhibitor market.

In December 2014, we entered into a global collaboration agreement with Pfizer for the development and commercialization of *SPK-FIX* product candidates for the treatment of hemophilia B. In July 2016, FDA granted breakthrough therapy designation to *SPK-9001,* the lead product candidate in our *SPK-FIX* program. In July 2018, we transitioned the program to Pfizer for Phase 3 development.

We are developing other liver-directed gene therapies, including *SPK-3006,* our lead product candidate for Pompe disease, an inherited lysosomal storage disorder caused by an enzyme deficiency that leads to accumulation of glycogen in cells, for which there are shortcomings in current enzyme replacement standard of care. In October 2018, we reported preclinical proof-of-concept data for *SPK-3006.*

SPK-7001 is our lead product candidate for the treatment of CHM, an IRD caused by mutations in the *REP-1* gene. We have completed enrollment of ten participants in two dose cohorts of our Phase 1/2 trial for *SPK-7001* and continue to follow subjects in the trial. In July 2017, we completed enrollment of five additional subjects in the trial who are at an earlier stage of disease. To date, *SPK-7001* has been well tolerated and we have not observed any product candidate-related SAEs in this trial. We have observed two SAEs that were deemed to be procedure related. We have received orphan product designation for *SPK-7001* for the treatment of CHM in both the United States and the European Union.

We have several product candidates in various stages of preclinical development. We have preclinical programs targeting IRDs, including Stargardt's disease. We are developing neurodegenerative disease product candidates that are intended to address TPP1 deficiency, which is a form of Batten disease, and Huntington's disease, among others. We have received orphan product designation in the United States for *SPK-TPP1* for the treatment of CLN2 disease (neuronal ceroid lipofuscinosis (NCL)) caused by TPP1 deficiency.

7

Table of Contents

Our product candidates

The following table summarizes information regarding our product candidates and development programs:

(1) Initial construct licensed from Genethon
(2) Form of Batten disease

Retina-directed gene therapies

Biallelic IRD due to RPE65 *mutations*

Background

Mutations in the *RPE65* gene lead to IRD characterized by a range of visual impairments, notably night blindness, or nyctalopia. The *RPE65* gene encodes a protein that helps convert the light entering the eye into electrical signals that are transmitted to the brain, enabling sight. Without the properly functioning protein encoded by the *RPE65* gene, the visual cycle is disrupted, resulting in debilitating visual impairments, progressing to blindness. The *RPE65* gene is expressed in the retinal pigment epithelium, or RPE, layer of the retina.

RPE65-mediated IRD

RPE65-mediated IRD historically has been clinically diagnosed based on clinical presentation and findings and has been characterized most frequently as a form of Leber congenital amaurosis, or LCA, or retinitis pigmentosa, or RP, among over 20 other clinical classifications. We estimate that LCA affects approximately one in every 81,000 individuals and RP affects approximately one in every 4,500 individuals. Because, prior to the approval of LUXTURNA, there were no pharmacologic treatments for IRDs and there are known to be over 220 different genes causing IRDs, there are limited epidemiology data from which to derive population estimates. Additionally, epidemiology estimates vary based on geography. We are aware of studies that estimate the prevalence of *RPE65* mutations within the LCA population from approximately 6% to 16% and within the RP population from approximately 1% to 3%. Based on our own assessment of the epidemiology data, we believe the prevalent population is up to approximately 6,000 individuals with *RPE65* mutations in the United States, Europe and select additional markets in the Americas and Asia/Pacific. We estimate the United States prevalent population at approximately 1,000 to 2,000 individuals.

Table of Contents

LUXTURNA (voretigene neparvovec)

In December 2017, FDA approved LUXTURNA (voretigene neparvovec-rzyl) for the treatment of patients with confirmed biallelic *RPE65* mutation-associated retinal dystrophy and viable retinal cells. LUXTURNA is the first FDA-approved gene therapy for a genetic disease, the first and only pharmacological treatment for an IRD and the first AAV vector gene therapy approved in the United States. LUXTURNA is manufactured at our manufacturing facility located in Philadelphia, which is the first licensed manufacturing facility in the United States for a gene therapy treating an inherited disease. LUXTURNA has received orphan drug status. In January 2018, we entered into a license and commercialization agreement with Novartis for the development and commercialization of voretigene neparvovec outside the United States. In November 2018, we received approval from the EMA for the marketing authorization of LUXTURNA in all 28-member states of the EU, as well as Iceland, Liechtenstein and Norway.

In October 2015, we announced positive top-line results from our pivotal Phase 3 clinical trial of LUXTURNA, the first successfully completed randomized controlled Phase 3 trial of a gene therapy for genetic disease in the United States. The Phase 3 trial demonstrated a statistically significant improvement of functional vision in subjects that were progressing toward complete blindness.

LUXTURNA continues to demonstrate durable effects as measured by both the multi-luminance mobility test, or MLMT, and full-field light sensitivity threshold testing, or FST.

We are supporting the appropriate use of LUXTURNA in the United States through small, targeted commercial and medical affairs teams to continue to build and promote access to the product. LUXTURNA is administered by trained retinal surgeons at selected treatment centers in the United States that specialize in treating IRDs.

In January 2018, we announced two novel payer programs to help ensure eligible patients in the United States have access to LUXTURNA: (i) an innovative contracting model that includes an option for direct-to-payer contracting; and (ii) an outcomes-based rebate arrangement with a short-term efficacy measure and a long-term durability measure. Traditionally, specialty medications administered by physicians in hospitals in the United States are purchased by the institution where the patient is treated. The institution then bills the payer, typically including a mark-up on the product. With higher-value, higher-cost therapies, this traditional “buy and bill” model may represent a significant financial burden and risk to the institution and may create substantial additional costs to the payer. Under our innovative contracting model, we enter into an agreement with the commercial payer under which the payer, or a designated specialty pharmacy, purchases LUXTURNA. As a part of this agreement, the payer agrees to provide coverage for its members consistent with FDA labeling of LUXTURNA, expedite benefits processing and cap patient out-of-pocket amounts at in-network limits. Further, we will share risk with certain health insurers by paying rebates if patient outcomes fail to meet specified thresholds, thereby linking the payment for LUXTURNA to both short-term efficacy (30-90 days) and longer-term durability (30 months) measures that are unique to this one-time gene therapy. The short-term and long-term measures will be based on FST testing scores, with a baseline to be established for each eligible patient before administration of LUXTURNA.

We have established Spark Therapeutics Generation Patient Services^{SM} to support commercially insured patients and their caregivers in the United States through the treatment experience. Through this program, we will assist eligible and enrolled commercially insured patients in navigating the insurance process, and will provide options to support their travel and accommodation logistics and costs to and from treatment centers, as well as assistance with other out-of-pocket costs directly related to the treatment.

SPK-7001 for the treatment of choroideremia

Overview

Choroideremia is an IRD linked to the X-chromosome. Clinically, CHM manifests in affected males in childhood as night blindness and a reduction of visual field, followed by progressive constriction of visual fields. CHM is characterized by deletions or mutations in the *CHM* gene, resulting in defective or absent Rab escort protein-1, which is the encoded protein of the *CHM* gene. We estimate prevalence of CHM is between approximately one in 50,000 and one in 100,000 people, implying a total population of up to approximately 12,500 males in the United States and the five major European markets.

SPK-7001

Our *SPK-CHM* program is technically similar to our LUXTURNA program, including use of the same vector, targeting the same types of RPE cells and utilizing the same route of administration through sub-retinal injection. *SPK-7001* is our investigational product candidate for the treatment of IRD caused by *CHM* gene mutations. We have received orphan product designation for *SPK-7001* in both the United States and the European Union.

Table of Contents

Phase 1/2 clinical trial

We have completed enrollment of ten participants in two dose cohorts of our Phase 1/2 trial for *SPK-7001* and continue to follow subjects in the trial. In July 2017, we completed enrollment of five additional subjects in the trial who are at an earlier stage of disease. To date, *SPK-7001* has been well tolerated and we have not observed any product candidate-related SAEs in this trial. We have observed two SAEs that were deemed to be procedure related. We are evaluating efficacy primarily by assessing functional vision, as measured by standard ophthalmic tests. Evaluations are ongoing.

Other IRDs

The *RPE65* and *CHM* genes are two of more than 220 genes that have been identified to cause IRDs. We have several preclinical programs targeting other IRDs, including a preclinical program addressing Stargardt's disease, an IRD that affects approximately 30,000 people in the United States.

Liver-directed gene therapies

Our product development portfolio includes product candidates targeting expression of genes in the liver, with a focus on hemophilia and lysosomal storage disorders.

Hemophilia B

Background

Hemophilia B is a serious and rare inherited disease characterized by insufficient blood clotting that results from the lack of functional FIX, a blood clotting factor normally produced by cells located in the liver. Hemophilia B is caused by mutations in the gene that encodes the coagulation FIX protein. The condition can lead to repeated and sometimes life-threatening episodes of spontaneous bleeding. According to the 2016 World Federation of Hemophilia Annual Global Survey, approximately 30,000 people worldwide suffer from hemophilia B.

The severity of hemophilia B is determined by the circulating levels of FIX. Severe hemophilia B is classified as a level of FIX in the blood of less than 1% of normal. People with severe hemophilia B experience frequent spontaneous bleeding episodes, often into their joints and muscles. Moderate hemophilia B is classified as a level of FIX in the blood equal to or greater than 1% of normal but less than 5% of normal. People with moderate hemophilia B may have bleeds following trauma, or may have spontaneous bleeding episodes, but these will occur less frequently than in those with severe hemophilia B.

The current standard of care for hemophilia B is either prophylactic or on-demand FIX protein replacement therapy, in which frequent intravenous administrations of recombinant FIX are required to stop or prevent bleeding. Prophylactic therapy for hemophilia B, which has been shown to lead to the best outcomes, is practiced only by some adult patients in the United States due to the significant expense, patient inconvenience and concern about lifetime insurance caps. A gene therapy treatment could offer patients the benefits of prophylaxis without the need for frequent factor infusion.

SPK-9001*, our lead* SPK-FIX *product candidate for the treatment of hemophilia B*

In December 2014, we entered into a global collaboration agreement with Pfizer for the development and commercialization of product candidates in our *SPK-FIX* program for the treatment of hemophilia B. Under this collaboration, we had responsibility for the clinical development of *SPK-FIX* product candidates through the completion of Phase 1/2 trials. Pfizer has responsibility for further clinical development, regulatory approvals and commercialization. Based on positive Phase 1/2 study results, in July 2018 we transitioned the program to Pfizer. In July 2018, Pfizer announced the initiation of a Phase 3 program.

Hemophilia A

Background

Hemophilia A is a serious and rare inherited disease characterized by insufficient blood clotting that results from the lack of functional factor VIII, a blood clotting factor normally produced by cells located in the liver. Hemophilia A is caused by mutations in the gene that encodes the coagulation factor VIII protein. The condition can lead to repeated and sometimes life-threatening episodes of spontaneous bleeding. According to the 2016 World Federation of Hemophilia Annual Global Survey, approximately 150,000 people worldwide suffer from hemophilia A.

The severity of hemophilia A is determined by the circulating levels of factor VIII. Severe hemophilia A is classified as a level of factor VIII in the blood of less than 1% of normal. People with severe hemophilia A experience frequent

spontaneous bleeding episodes, often into their joints and muscles. Moderate hemophilia A is classified as a level of factor VIII in the blood

Table of Contents

equal to or greater than 1% of normal but less than 5% of normal. People with moderate hemophilia A may have bleeds following trauma, or may have spontaneous bleeding episodes, but these will occur less frequently than in those with severe hemophilia A.

The current standard of care for hemophilia A is either prophylactic or on-demand factor VIII protein replacement therapy, in which frequent intravenous administrations of recombinant factor VIII are required to stop or prevent bleeding. Prophylactic therapy for hemophilia A, which has been shown to lead to the best outcomes, is practiced only by some adult patients in the United States due to the significant expense, patient inconvenience and concern about lifetime insurance caps. A gene therapy treatment could offer patients the benefits of prophylaxis without the need for frequent factor infusion.

The most significant complication of treatment with FVIII concentrates in patients with hemophilia A is the development of alloantibodies, or inhibitors, that block factor VIII activity. Approximately 30% of hemophilia A patients develop inhibitors to recombinant or plasma-derived factor VIII. Children, people with a family history of inhibitors and certain ethnic subgroups are more at risk for developing inhibitors, but it has not been possible to predict in advance which patients will be affected. Inhibitors usually appear in young children, within the first 50 exposure days to FVIII replacement therapy, but they can develop at any age.

Severe hemophilia patients with inhibitors do not bleed more often than other severe patients, but their bleeds are more difficult to manage because they do not respond to standard treatment. Inhibitor patients also may develop serious complications like uncontrollable bleeds and joint disease. Patients with inhibitors are hospitalized more frequently.

Once factor replacement is ineffective due to inhibitors, acute management of bleeding requires agents that bypass factor VIII activity. Long-term management traditionally has consisted of eradicating inhibitors through immune tolerance. Immune tolerance induction, or ITI, can be achieved in approximately 70% of patients that receive regular infusions of factor VIII, which are given several times per week over periods ranging up to 18 months. These frequent infusions may require the placement of an indwelling line, particularly in younger children. Despite the development of multiple ITI protocols over the past forty years, the mechanism of tolerance induction and the best means of achieving it are unknown. Given the arduous nature of all ITI protocols, the time commitment required from families to implement it and the substantial failure rate, some have advocated abandoning this approach and managing inhibitor patients solely with newer, long-acting bypassing agents. Others note that eradication of the inhibitor leads to better overall outcomes and should still be pursued.

SPK-8011*, our lead* SPK-FVIII *product candidate for the treatment of hemophilia A*

We initiated a dose-escalating Phase 1/2 clinical trial for our lead product candidate, *SPK-8011*, in 2017. In February 2018, FDA granted breakthrough designation to *SPK-8011*. We recently initiated a Phase 3 clinical program for *SPK-8011*, beginning with a run-in study. We retain global commercialization rights to the *SPK-FVIII* program.

As of a November 2, 2018, data cutoff date, we had enrolled 12 participants in the trial - two at a dose of 5×10^{11} vg/kg of body weight, three at a dose of 1×10^{12} vg/kg and seven at a dose of 2×10^{12} vg/kg. Across all 12 participants at the three doses tested, we saw a 94% reduction in bleeding and a 95% reduction in infusions. In the 2×10^{12} vg/kg dose cohort, five of the seven participants had reduced their overall bleeds and infusions by 100% and 99% , respectively (calculated based on data after week four). We also saw evidence of stable, durable factor VIII activity levels in all participants that have been followed for greater than one year. We demonstrated a dose response, with higher doses, on average, leading to higher factor VIII levels. No participant developed factor VIII inhibitors, no thromboembolic events have been reported and transaminase elevations were infrequent and transient. One participant was electively admitted to the hospital to receive intravenous administration of methylprednisolone rather than having the infusions on an outpatient basis. This admission met the criteria for an SAE. We plan to incorporate a course of prophylactic steroids going forward in the development program.

Across the study, seven of the 12 participants received a tapering course of oral steroids in response to an alanine aminotransferase, or ALT, elevation above participant baseline, declining factor VIII levels and/or positive IFN-gamma enzyme-linked immunospots, or ELISPOTs. For these seven participants, steroids led to a normalization of ALT levels and ELISPOTs. For all but two participants in the 2×10^{12} vg/kg dose cohort, oral steroids led to a

stabilization of factor VIII levels. One of these two participants did not rapidly respond to oral steroids and was electively admitted to the hospital to receive two intravenous infusions of methylprednisolone rather than having the infusions on an outpatient basis. The event subsequently resolved, but the admission to the hospital met the criteria for an SAE. We plan to incorporate a course of prophylactic steroids going forward in the development program.

We have scaled our mammalian cell-based suspension process to a 400 liter process and have achieved initial yields that are supportive of our future clinical and commercial requirements. Analytical and non-clinical testing demonstrated the comparability of material manufactured with this suspension process to material manufactured with our adherent process. We have secured dedicated manufacturing capacity at Brammer Bio's facility in Cambridge, Massachusetts.

Table of Contents

SPK-8016 *for the treatment of hemophilia A patients with inhibitors*

We have additional product candidates in the *SPK-FVIII* program that are intended to target specific sub-populations of hemophilia A patients, the first of which will be aimed at addressing the hemophilia A inhibitor market using a novel, internally developed product candidate, *SPK-8016*. Our IND for *SPK-8016* has been cleared and, per agreement with FDA, we initiated dosing this Phase 1/2 trial in a cohort similar to our on-going *SPK-8011* Phase 1/2 trial in order to establish safety before expanding into participants representing segments of the inhibitor market.

SPK-3006 ***for the treatment of Pompe disease***

We are developing other liver-directed gene therapies, including *SPK-3006,* for Pompe disease. Pompe disease is an inherited lysosomal storage disorder caused by an enzyme deficiency that leads to accumulation of glycogen in cells. Pompe disease is a progressive condition that can lead to muscle weakness making walking, breathing and simple activities difficult.

In October 2018, we presented preclinical proof of concept data for our lead investigational product candidate, *SPK-3006*. *SPK-3006* is an AAV gene therapy expressing a novel, modified form of GAA (secGAA) engineered for efficient secretion into plasma. Preclinical data demonstrated glycogen clearance throughout the body, including in refractory tissues, with sustained plasma GAA levels and evidence of lysosomal uptake driven by one-time administration.

CNS-directed gene therapies

We are developing neurodegenerative disease product candidates that are intended to address TPP1 deficiency, which is a form of Batten disease, and Huntington's disease, among others. We have received orphan product designation in the United States for *SPK-TPP1* for the treatment of CLN2 disease (neuronal ceroid lipofuscinosis (NCL)) caused by TPP1 deficiency.

TPP1 deficiency is a form of Batten disease that causes severe childhood neurodegenerative disorders that result in motor and mental decline, seizures and visual deficits appearing between ages two and four and that is fatal by ages ten to twelve in a majority of cases.

Huntington's disease is a hereditary genetic disorder with negative physical, emotional, behavioral and cognitive effects.

We have other neurodegenerative disease programs in preclinical development.

Our manufacturing platform

Using a chemical method we refer to as transfection, we insert many copies of DNA plasmids encoding the specific therapeutic gene sequence, or transgene, into human embryonic kidney cells that have already been grown to high density. During an incubation period following transfection, each cell produces vectors through biosynthesis using the natural machinery available within the cell. At the end of the incubation period, the newly generated vectors are collected from the cells that have been broken apart or, alternatively, from the cell culture medium.

We have made significant investments in developing optimized manufacturing processes and believe that our processes and methods provide the most comprehensive manufacturing process developed to date for AAV-based vector therapies, including:

- sufficient scale to support commercial manufacturing requirements for LUXTURNA and many of our product candidates, including those for IRDs;
- stable manufactured AAV vectors with sufficient longevity so that a small number of initial batches will likely provide adequate commercial supply for multiple years;
- proprietary AAV vector manufacturing processes and techniques that produce a highly purified product candidate, as evidenced by the approximately 25- to 30-fold reduction in non-infectious vector related impurities as compared to vectors used in many previous clinical trials;

- approximately 30 assays to accurately characterize our process and the AAV vectors we produce; and

- a series of high-efficiency purification processes, adapted and customized for multiple different AAV capsids, which allow us to produce higher purity AAV vector solutions, with higher concentrations of active vectors and that are essentially free of empty capsids.

We believe these improvements, and our continued investment in our manufacturing platform, will enable us to develop best-in-class, next-generation gene therapy products. For example, we recently demonstrated proof-of-concept in scaling from

Table of Contents

the current adherent process to a suspension process. This capability will be important in addressing disease indications with a large target population, such as hemophilia A.

In 2017, we received FDA current good manufacturing practices, or cGMP, validation of our facility in Philadelphia to produce commercial supply of LUXTURNA. In 2018, we successfully completed EMA inspection of our manufacturing facility in Philadelphia. Our facility in Philadelphia is the first licensed manufacturing facility in the United States for a gene therapy treating an inherited disease and is now licensed in Europe and all mutual recognition countries.

Intellectual property

We strive to protect and enhance the proprietary technology, inventions and improvements that are commercially important to the development of our business, including by seeking, maintaining and defending patent rights, whether developed internally or licensed from third parties. We also rely on trade secrets relating to our proprietary technology platform and on know-how, continuing technological innovation and in-licensing opportunities to develop, strengthen and maintain our proprietary position in the field of gene therapy. Additionally, we intend to rely on regulatory protection afforded through orphan drug designations, data exclusivity and market exclusivity as well as patent term extensions, where available.

Our future commercial success depends, in part, on our ability to: obtain and maintain patent and other proprietary protection for commercially important technology, inventions and know-how related to our business; defend and enforce our patents; preserve the confidentiality of our trade secrets; and operate without infringing the valid enforceable patents and proprietary rights of third parties. Our ability to stop third parties from making, using, selling, offering to sell or importing our products may depend on the extent to which we have rights under valid and enforceable patents or trade secrets that cover these activities. With respect to both our owned and licensed intellectual property, we cannot be sure that patents will issue with respect to any of the pending patent applications to which we license rights or with respect to any patent applications that we or our licensors may file in the future, nor can we be sure that any of our licensed patents or any patents that may be issued in the future to us or our licensors will be commercially useful in protecting our product candidates and methods of manufacturing the same. Moreover, we have not sought, and may be unable to obtain, patent protection for certain of our product candidates generally, including *SPK-CHM*, as well as with respect to certain indications. See “Risk factors—Risks related to our intellectual property” for a more comprehensive description of risks related to our intellectual property.

We have licensed numerous patents and patent applications and possess substantial know-how and trade secrets relating to our product candidates. Our proprietary intellectual property, including patent and non-patent intellectual property, generally is directed to AAV vectors, methods of treatment of clinical indications important for our development programs, transferring genetic material into cells, inhibiting antibody responses to gene therapies, processes to manufacture and purify our AAV- and lentiviral-based product candidates and other proprietary technologies and processes related to our lead product candidates. We are heavily dependent on the patented or proprietary technologies that we license from third parties. We anticipate that we will require additional licenses to third-party intellectual property rights relating to our development programs in the future, which may not be available on commercially reasonable terms, if at all.

Licensed patents and patent applications

As of February 20, 2019, our patent portfolio included U.S. and foreign patents and patent applications licensed from The Children's Hospital of Philadelphia, or CHOP, the University of Iowa Research Foundation, or UIRF, The University of Pennsylvania, or Penn, Genethon, Inc., or Genethon, and the U.S. National Institutes of Health, or NIH. Our patent portfolio also includes patent applications that we have filed on our own technologies, including technologies related to our hemophilia A program and our manufacturing technologies. The patents and patent applications in our patent portfolio cover technology used in our own development programs, as well as technology used in our collaboration with Pfizer. We have granted Pfizer an exclusive worldwide license for the development and commercialization of product candidates for the treatment of hemophilia B under the patents and other rights listed below that relate to our *SPK-FIX* program.

Manufacturing platform

We exclusively in-license three patent application families from CHOP relating to scalable manufacturing for producing high-purity gene therapy vectors. The first family relates to manufacture of our own product candidates as well as the product candidates and development programs that are the subject of our collaboration with Pfizer, and patents have been granted in the United States, Europe, Australia and Mexico. These patents will expire in 2031, excluding any potential patent term extension or adjustment. Corresponding patent applications are pending in the United States, Brazil, Canada, China, Israel, India and Japan. We expect that patents issuing from these applications would expire in 2031, excluding any potential patent term extension or adjustment. The second and third application families relate to scalable manufacturing and purification of lentiviral vectors. The second application family is pending in the United States, Australia, Canada, Europe, Hong Kong and Japan. We expect that patents issuing from these applications, if any, would expire in 2032, excluding any potential patent term extension or adjustment. The third application family has been granted in Europe. This patent will expire in 2034, excluding any

Table of Contents

potential patent term extension or adjustments. Corresponding patent applications are pending in the United States, Australia, Brazil, Canada, China India, Israel, Japan, Mexico, Russia, South Africa and South Korea. We expect that patents issuing from these applications, if any, would expire in 2034, excluding any potential patent term extension or adjustment.

We also have filed patent applications relating to manufacturing technologies that we have developed, including:

- A patent application family relating to reduced AAV vector aggregation during manufacturing. This application family is pending in Australia, Brazil, Canada, China, Europe, Indonesia, Israel, India, Japan, Malaysia, Mexico, New Zealand, Russia, Saudi Arabia, Singapore, South Africa and South Korea. We expect that any patents issuing from these applications will expire in 2037, excluding any potential patent term extension or adjustment.

- A patent application family relating to improvements in AAV vector purification. This application family is pending in Australia, Brazil, Canada, Chile, China, Colombia, Europe, India, Indonesia, Israel, Japan, Malaysia, Mexico, New Zealand, Peru, Philippines, Russia, Saudi Arabia, Singapore, South Africa, South Korea and the United States. We expect that any patents issuing from these applications will expire in 2037, excluding any potential patent term extension or adjustment.

- A patent application family relating to a novel cell line for AAV vector production. This application family is pending in Australia, Brazil, Canada, China, Europe, Japan, Mexico, New Zealand, Saudi Arabia, Singapore, South Africa, South Korea and the United States. We expect that any patents issuing from these applications will expire in 2037, excluding any potential patent term extension or adjustment.

- A patent application family relating to cell transfection improvements for AAV vector production. This application family is pending in Australia, Brazil, Canada, China, Colombia, Europe, Hong Kong, India, Indonesia, Israel, Japan, Malaysia, Mexico, New Zealand, Peru, Philippines, Russia, Saudi Arabia, Singapore, South Africa, South Korea and the United States. We expect that any patents issuing from these applications will expire in 2036, excluding any potential patent term extension or adjustment.

- A Patent Cooperation Treaty, or PCT, patent application relating to cell transfection improvements for AAV vector production. We expect that any patents issuing from this application will expire in 2038, excluding any potential patent term extension or adjustment.

- A PCT patent application relating to improvements in AAV vector purification. We expect that any patents issuing from this application will expire in 2038, excluding any potential patent term extension or adjustment.

- A U.S. patent application relating to cell line for AAV vector production. We expect that any patents issuing from this application will expire in 2039, excluding any potential patent term extension or adjustment.

We refer to these CHOP manufacturing-related patents and patent applications together with our manufacturing-related patent applications as our “manufacturing patent applications.”

Modified AAV vectors and gene delivery

We are developing additional technology in a number of different areas to improve or expand upon our current product candidates. These include technologies exclusively licensed from CHOP that are generally related to modifying gene therapy vectors, adding a companion therapy or diagnostic or developing other therapeutic genes, and technologies that we have developed. The licensed and Spark-owned patent rights underlying these technologies include:

- Six U.S. patent applications that relate to alternate, or modified, AAV vectors for gene delivery that we believe have certain technical advantages that are broadly applicable to all of our current, and potentially to our future, clinical

programs, including transducing certain target cells, modifications to AAV vectors, modifying AAV vectors to reduce antibody binding, and producing reduced amounts of contaminating AAV particles. We expect that patents issuing from these applications, if any, would expire from 2028 up until 2034, excluding any potential patent term extension or adjustment.

- Two pending U.S. patent applications that generally relate to inhibiting immune responses to AAV vector and measuring antibodies that bind to AAV. We expect that patents issuing from these applications, if any, would expire between 2032 and 2034, excluding any potential patent term extension or adjustment.

Table of Contents

- A pending U.S. patent application that generally relates to improvements to measuring antibodies that bind to AAV. We expect that patents issuing from this application, if any, would expire in 2039, excluding any potential patent term extension.

- A pending U.S. patent application that generally relates to novel capsid technologies. We expect that patents issuing from this application, if any, would expire in 2039, excluding any potential patent term extension.

- Two pending U.S. patent applications that generally relate to modulating immune responses for AAV therapies. We expect that patents issuing from this application, if any, would expire in 2039, excluding any potential patent term extension.

We believe our manufacturing patent applications and related know-how and trade secrets may provide us with additional intellectual property protection relating to our planned use of these technologies.

Retina-directed therapies

In December 2015, we converted a co-exclusive in-license from Penn of certain rights to a U.S. patent co-owned by Penn, Cornell University and the University of Florida that relates to methods of treating patients with LCA due to *RPE65* mutations to an exclusive license in the field of use related to the treatment of retinal disorders or diseases caused by a mutation or mutations in the *RPE65* gene. This patent is expected to expire in 2022, excluding any potential patent term extension or adjustment. There are no issued patents or pending patent applications outside of the United States that correspond to this patent.

We also in-licensed from CHOP U.S. and PCT patent applications co-owned by CHOP and Penn relating to testing functional vision with a mobility course, which can be used as an assessment tool to assess improvements in vision following treatment of an IRD. We expect that any patents issuing from these applications would expire in 2034, excluding any potential patent term extension or adjustment.

We believe our manufacturing patent applications and related know-how and trade secrets may provide us with additional intellectual property protection relating to LUXTURNA and *SPK-CHM*.

Liver-directed gene therapies

We exclusively in-licensed certain patents and patent applications from CHOP related to our hemophilia programs. In general, these patents and patent applications relate to AAV-mediated gene therapy, adjunct therapy to use with gene therapy treatment, modified AAV vectors and modified forms of factor VIII. These licensed patent rights include:

- A patent application family relating to modified AAV vectors for delivery of factor IX. This application is granted in the U.S. and Singapore. These patents will expire in 2034, excluding any potential patent term extension or adjustment. Corresponding patent applications are pending in Australia, Brazil, Canada, China, Colombia, Europe, Hong Kong, India, Indonesia, Israel, Japan, Malaysia, Mexico, New Zealand, Peru, Philippines, Russia, Saudi Arabia, South Africa and South Korea. We expect that any patents issuing from these applications will expire in 2034, excluding any potential patent term extension or adjustment.

- A U.S. patent relating to an adjunct therapy to reduce inhibitory antibodies against factor IX administered via gene therapy. This patent will expire in 2020, excluding any potential patent term extension or adjustment.

- A U.S. patent application relating to certain modifications to a *FIX* gene that enhances secretion of factor IX. We expect that any patents issuing from this application will expire in 2021, excluding any potential patent term extension or adjustment.

- A U.S. patent application relating to modified factor IX expression cassettes. We expect that any patents issuing from this application will expire in 2036, excluding any potential patent term extension or adjustment. Corresponding patent applications are pending in Australia, Brazil, Canada, China, Colombia, Europe, Hong Kong, India, Indonesia, Israel, Japan, Malaysia, Mexico, New Zealand, Peru, Philippines, Russia, Saudi Arabia, Singapore, South Africa and South Korea. We expect any patents issuing from these applications will expire in 2036, excluding any potential

patent term extension or adjustment.

- A U.S. patent relating to a factor VIII heavy chain with enhanced secretion. This patent will expire in 2023, excluding any potential patent term extension or adjustment. There are no issued patents or pending patent applications outside of the United States that correspond to this U.S. patent.

Table of Contents

- U.S. patents relating to factor VIII variants having enhanced coagulation. These patents will expire in 2030, excluding any potential patent term extension or adjustment. A corresponding patent is issued in Australia. This patent will expire in 2030, excluding any potential patent term extension or adjustment. Corresponding patent applications are pending in Canada and Europe. We expect any patents issuing from these applications will expire in 2030, excluding any potential patent term extension or adjustment.

We also have filed patent applications relating to our *SPK-FVIII* program on technologies which we have developed, including:

- A U.S. patent application relating to modified factor VIII expression constructs. We expect that any patents issuing from this application will expire in 2036, excluding any potential patent term extension or adjustment. Corresponding patent applications are pending in Australia, Brazil, Canada, Chile, China, Colombia, Europe, Hong Kong, India, Indonesia, Israel, Japan, Malaysia, Mexico, New Zealand, Peru, Philippines, Russia, Saudi Arabia, Singapore, South Africa and South Korea. We expect any patents issuing from these applications will expire in 2036, excluding any potential patent term extension or adjustment.

- A PCT patent application relating to AAV gene therapy treatment of hemophilia A. We expect that any patents issuing from this application will expire in 2038, excluding any potential patent term extension or adjustment.

- A U.S. patent application relating to modified factor VIII expression constructs. We expect that any patents issuing from this application will expire in 2039, excluding any potential patent term extension or adjustment.

We also have exclusively in-licensed three patent application families from Genethon relating to our Pompe program, including:

- A U.S. patent application relating to certain Pompe constructs. We expect that any patents issuing from this application will expire in 2038, excluding any potential for patent term extension or adjustment. Corresponding patent applications are pending in Australia, Brazil, Canada, China, Europe, Japan, and Mexico.

- Two U.S. patent application relating to certain Pompe constructs. We expect that any patents issuing from this application will expire in 2038, excluding any potential for patent term extension or adjustment. Each of these U.S. patent applications has corresponding patent applications pending in Australia, Brazil, Canada, Chile, China, Colombia, Europe, India, Indonesia, Israel, Japan, Malaysia, Mexico, New Zealand, Peru, Philippines, Russia, Saudi Arabia, Singapore, South Africa, and South Korea.

We also have filed a U.S. patent application on certain Pompe constructs which we have developed. We expect that any patents issuing from this application will expire in 2039, excluding any potential for patent term extension or adjustment.

We believe our manufacturing patent applications and related know-how and trade secrets may provide us with additional intellectual property protection relating to our *SPK-FIX* program, *SPK-FVIII* program and *SPK-GAA* program.

CNS-directed gene therapies

We exclusively in-licensed a portfolio of approximately 181 U.S. and foreign patents and patent applications from UIRF that relate to treatment of a broad array of CNS and neurodegenerative diseases.

Trade secrets

In addition to patents and licenses, we rely on trade secrets and know-how to develop and maintain our competitive position. For example, significant aspects of our AAV and lentiviral vector and manufacturing processes and gene therapies are based upon trade secrets and know-how. However, trade secrets can be difficult to protect. We seek to protect our proprietary technology and processes, and obtain and maintain ownership of certain technologies, in part, through confidentiality agreements and invention assignment agreements with our employees, consultants, scientific advisors, contractors and commercial partners. We also seek to preserve the integrity and confidentiality of our data,

trade secrets and know-how including by implementing measures intended to maintain the physical security of our premises and the physical and electronic security of our information technology systems.

Table of Contents

Collaboration and license agreements

Pfizer

In December 2014, we entered into a global collaboration agreement with Pfizer for the development and commercialization of *SPK-FIX* product candidates in our gene therapy program for the treatment of hemophilia B. Under the agreement, we have granted Pfizer an exclusive worldwide license under specified patent rights and know-how relating to any factor IX gene therapy that we develop, manufacture or commercialize prior to December 31, 2024, to develop, manufacture and commercialize such licensed factor IX gene therapy products for the diagnosis, prevention, treatment and cure of hemophilia B.

Under the terms of the agreement, we are primarily responsible for conducting research and development activities through completion of Phase 1/2 clinical trials of hemophilia B product candidates. Pfizer and we will share development costs incurred under an agreed product development plan for each product candidate, with our share of development costs under the agreement limited to $10.6 million. Following the completion of Phase 1/2 clinical trials, Pfizer will primarily be responsible for development, manufacture, regulatory approval and commercialization, including all costs associated therewith.

During the period through completion of Phase 1/2 clinical trials, which we refer to as the collaboration period, the hemophilia B program will be governed by a joint steering committee, or JSC, consisting of representatives of Pfizer and us. The JSC will, among other responsibilities, provide operational and strategic oversight to the activities to be performed under the product development plan, will monitor and assess the progress of collaboration activities and will serve as a forum for the parties to communicate regarding collaboration issues and resolve disputes. During the collaboration period, if the JSC is unable to reach agreement, we generally have final decision-making authority regarding the conduct of the agreed product development plan and, following the collaboration period, Pfizer generally has final decision-making authority regarding the further development and commercialization of licensed compounds and licensed products.

Under the terms of the agreement, we received a $20.0 million upfront payment. In each of December 2015 and December 2016, we earned a $15.0 million milestone payment and also are eligible to receive up to an additional $230.0 million in aggregate milestone payments under the agreement, $110.0 million of which relates to potential development, regulatory and commercial milestones for the first product candidate to achieve each milestone and $120.0 million of which relates to potential regulatory milestones for additional product candidates. In addition, we are entitled to receive royalties, calculated as a low-teen percentage of net sales of licensed products. The royalties may be subject to certain reductions, including for a specified portion of royalty payments that Pfizer may become required to pay under any third-party license agreements, subject to a minimum royalty. Under the agreement, we remain solely responsible for the payment of license payments payable by us under specified license agreements.

In June 2016, Pfizer and we amended the agreement to allow for the technology transfer of certain of our manufacturing processes related to *SPK-9001* to be transferred to Pfizer for use in the field of hemophilia B.

In November 2017, Pfizer and we amended the agreement to provide for the enrollment of up to five additional participants in the current Phase 1/2 clinical trial each of which will receive *SPK-9001* manufactured using an enhanced process to test its comparability to *SPK-9001* received by the first 10 participants enrolled in the ongoing trial. Under the terms of this amendment, we received a $10.0 million upfront payment and received an additional $15.0 million in milestone payments.

The agreement will expire on a country-by-country basis upon the latest of: (i) the expiration of the last-to-expire valid claim, as defined in the agreement, in the licensed patent rights covering a licensed product, (ii) the expiration of the last-to-expire regulatory exclusivity granted with respect to a licensed product or (iii) 15 years after the first commercial sale of the last licensed product to be launched, in each case in the applicable country. The last to expire patent right licensed to Pfizer, if it issues as a patent, is currently expected to expire in 2034, excluding any applicable patent term extension or adjustment, although we could obtain rights to additional patents, including through the issuance of pending patent applications, with later expiration dates, which would be subject to Pfizer's license under the agreement. After expiration, but not termination, of the agreement as to a country, Pfizer's licenses will become fully paid-up, royalty-free, perpetual and irrevocable as to licensed products in the applicable country.

Pfizer may terminate the agreement, on a licensed product-by-licensed product and a country-by-country basis, or in its entirety, for any or no reason (i) upon 90 days' written notice prior to the commencement of commercialization of a licensed product or (ii) upon 180 days' written notice after the commencement of commercialization of a licensed product. Either party may, subject to a cure period, terminate the agreement in the event of the other party's uncured material breach. Either party also may terminate the agreement upon the occurrence of specified bankruptcy events. If the agreement is terminated, rights to licensed products that were being developed, manufactured or commercialized at that time generally revert to us.

If the agreement is terminated by Pfizer after the initiation of a pivotal clinical trial, and we continue development utilizing intellectual property rights or data developed by Pfizer through its activities under the agreement, we will be required to pay

Table of Contents

Pfizer a royalty, calculated as a single-digit percentage of net sales of licensed products, with the percentage determined based on the stage of development or commercialization of the product candidate at the time of Pfizer's termination.

In February 2018, we entered into a supply agreement with Pfizer for production of one batch of *SPK-9001* drug substance, which was delivered in July 2018.

In July 2018, Pfizer announced they had initiated a Phase 3 program following the transfer of our responsibility for the hemophilia B gene therapy program to Pfizer.

Novartis

In January 2018, we entered into a Licensing and Commercialization Agreement, or the Novartis License Agreement, with Novartis to develop and commercialize voretigene neparvovec outside the United States. We also entered into a Supply Agreement with Novartis, or the Novartis Supply Agreement, to manufacture and supply all of the requirements of Novartis for voretigene neparvovec. Under the terms of the Novartis License Agreement, we granted Novartis an exclusive right and license, under our intellectual property reasonably necessary or useful for the development or commercialization of LUXTURNA™, for the treatment, prevention, cure or control of *RPE65*-mediated IRD in humans outside the United States.

Novartis paid us a non-refundable, non-creditable, one-time payment of $105.0 million and $25.0 million for approval of voretigene neparvovec by the EMA in November 2018, and we may receive up to an additional $40.0 million based upon the achievement of certain aggregate net sales in certain markets. We also are entitled to receive royalty payments at a flat mid-twenties percentage of net sales on a royalty-region by royalty-region basis, subject to reduction and extension in certain circumstances. We will retain regulatory responsibility for obtaining approval for LUXTURNA by EMA and Novartis will have regulatory responsibility for obtaining approval for LUXTURNA for countries outside of the United States and the European Union.

The Novartis License Agreement continues until the last to complete royalty term, which is on a royalty-region by royalty-region basis for 12 years from the first commercial sale in such region of LUXTURNA, but may be extended in a certain country until regulatory exclusivity expires in that country or on a region-by-region basis until aggregate net sales fall below a certain threshold. Either party may terminate the Novartis License Agreement upon the other party's uncured material breach of the Novartis License Agreement, insolvency, or bankruptcy. Novartis may terminate the Novartis License Agreement at any time upon one year's prior written notice to us. Novartis also may terminate the Novartis License Agreement in the event: (i) that there is an uncured material breach of the Novartis Supply Agreement by us, resulting in Novartis taking over the manufacture of LUXTURNA or (ii) we undergo a change of control.

Under the Novartis Supply Agreement, we have agreed to provide all of the commercial supply of LUXTURNA required by Novartis, subject to certain conditions. The Novartis Supply Agreement continues until the expiration or early termination of the Novartis License Agreement. Either party also may terminate the Novartis Supply Agreement upon the other party's uncured material breach of the Novartis Supply Agreement, insolvency or bankruptcy.

In-license agreements

We have rights to use and exploit multiple issued and pending patents under licenses from other entities. We consider the commercial terms of these licenses, which provide for modest milestone and royalty payments, and their provisions regarding diligence, insurance, indemnification and other similar matters, to be reasonable and customary for our industry.

The Children's Hospital of Philadelphia

In October 2013, we entered into a technology assignment agreement with CHOP. Under this agreement, CHOP assigned to us CHOP's rights to the preclinical and clinical programs and intellectual property that we are currently advancing, as well as know-how, standard operating procedures, trade secrets and proprietary processes related to our manufacturing platform. Furthermore, under this agreement, we obtained commercial rights to the drug master file, batch records and related data associated with the manufacture of AAV and lentiviral vectors using our manufacturing platform.

We also entered into a license agreement with CHOP under which CHOP granted us an exclusive worldwide license in the field of gene therapy, with the right to sublicense, under a broad portfolio of gene therapy and viral vector patent rights and gene therapy know-how related to vector manufacturing technology, the treatment of hemophilia and other gene therapy indications. CHOP also granted us a non-exclusive worldwide license in the field of gene therapy, with the right to sublicense, to other know-how owned or controlled by CHOP, existing as of the effective date of the license agreement and not explicitly covered by the exclusive licenses, that is necessary or useful for making, using, selling or importing any products we may develop that are covered by our exclusive license. Under both license grants, we have the right to research, develop, manufacture and commercialize products covered by the licensed patent rights or the licensed know-how in the field of gene therapy. Under the terms of the license agreement, we are obligated to use commercially reasonable best efforts to develop and

Table of Contents

commercialize licensed products. We are obligated under the license agreement to make milestone payments upon the treatment of the first subject treated in a U.S. Phase 3, or a foreign equivalent, clinical trial and upon the first commercial sale for the first licensed product in each of four indications. These milestone payments range from $125,000 to $5.0 million, and would, in the aggregate, reach a maximum of $7.1 million if all milestones are achieved. In addition, we are obligated to pay CHOP a low-single-digit royalty on a country-by-country basis on net sales of licensed products covered by a valid licensed patent claim. Following the expiration of our royalty obligations as to a licensed product in a country, we will retain a perpetual, full and unrestricted right to make, use and commercialize the licensed product in such country under the licensed intellectual property rights. CHOP controls the prosecution and maintenance of the licensed patent rights. We have agreed to reimburse CHOP for fees and expenses incurred in connection with the prosecution and maintenance of the licensed patent rights, including those fees and expenses incurred prior to the effective date of the license agreement. Unless sooner terminated, the term of the license agreement continues until the expiration of the last to expire of the licensed patent rights, the latest of which is currently expected to expire in 2034. If we oppose or contest the grant or validity of any licensed patent right, or any claims thereof, CHOP may terminate the license granted to us with respect to such patent right. CHOP may terminate this license upon uncured material breaches by us of the terms of the license or if such action is legally necessary to comply with applicable federal laws or regulations relating to government march-in rights and we may terminate the license at any time upon giving 90 days' prior written notice to CHOP.

We also have entered into a master research services agreement with CHOP under which CHOP supplies us with viral vectors. Under this master research services agreement, we expect to maintain a sufficient supply of clinical-grade gene therapy vectors produced in CHOP's cGMP clinical facility to meet both our clinical needs and, at our option, our commercial batches to support the commercial launch of LUXTURNA. The term of the agreement extends until October 14, 2028 as to services relating to the supply of *RPE65* vectors and until June 30, 2018 as to other services, and continues beyond such expiration dates as to work orders executed by the parties prior to the applicable expiration date until the completion of such work orders. We amended this agreement in March 2016 to extend the expiration date for services other than the supply of LUXTURNA vectors. We may terminate this agreement upon 30 days' written notice for any reason, and CHOP may terminate this agreement upon 30 days' written notice upon uncured material breaches by us of the terms of the agreement or if it reasonably determines that continuation of this agreement will have a materially adverse effect on its legal, regulatory or tax status.

We also entered into an additional licensing agreement with CHOP in November 2015. The licensing agreement supplements our existing license agreement with CHOP by granting us a worldwide exclusive license, with the right to sublicense, to use and practice a patent application family related to the production of gene therapies on substantially the same terms and conditions as the existing agreement.

University of Pennsylvania

In December 2015, we converted a co-exclusive license agreement to certain patent rights with Penn, Cornell University and the University of Florida relating to a method of treating and retarding the development of blindness to manufacture and commercialize products covered by the licensed patent rights in the field of research, development, manufacture and commercialization for the diagnosis, treatment, amelioration and prevention of human and animal diseases to an exclusive license in the field of use related to the treatment of retinal disorders or diseases caused by a mutation or mutations in the *RPE65* gene. Penn can no longer grant an additional license to a third party with the same scope of rights that we have received under our amended license agreement with Penn, including a right to commercialize products covered by the licensed patent rights.

Under the terms of the license agreement, we are obligated to use commercially reasonable efforts to develop and commercialize licensed products, and to use such efforts to accomplish specified development and commercial launch objectives in accordance with a specified timeline as well as to expend specified resources in the development and commercialization of licensed products. If our total expenditures on development and commercialization of the licensed products in any 12-month period do not meet or exceed the applicable diligence minimum, then we must pay Penn the amount of the shortfall. Under the terms of the agreement, we are obligated to make commercial milestone payments related to the licensed products, which could, in the aggregate, reach a maximum of $3.8 million per licensed product if all milestones are achieved for such licensed product. In addition, we are obligated to pay Penn a

low- to mid-single-digit royalty, on a country-by-country basis, on net sales of licensed products covered by a valid licensed patent claim. Penn controls the prosecution and maintenance of the licensed patent rights. We made an initial cash payment to Penn to cover 50% of Penn's previously incurred patent expenses relating to the licensed patent rights, with the exception of one patent for which we agreed to reimburse Penn for all such expenses. With respect to that specific patent, we agreed to reimburse Penn for patent expenses arising during the term of the license. This license will expire upon the expiration or abandonment of all of the patents and patent applications subject to the license, the latest of which is currently expected to expire in 2022. Penn may terminate the license upon uncured material breaches by us of the terms of the license or upon the occurrence of certain events, including specified bankruptcy and insolvency events relating to us, or if we commence an action against Penn or any of the co-owners of the licensed patent rights

Table of Contents

to declare or render invalid or unenforceable the patent rights. We may terminate the license at any time upon giving 60 days' prior written notice to Penn.

In December 2014, we entered into a license agreement with Penn, under which Penn granted us an exclusive, worldwide license, with the right to sublicense, to certain patent rights owned by Penn related to certain proviral plasmids that are useful in the manufacture of certain gene therapy products for the treatment of CHM.

Under the terms of the license agreement, we are obligated to use commercially reasonable efforts to develop and commercialize licensed products, and to use such efforts to accomplish development and commercial launch objectives as well as to expend specified resources in the development and commercialization of licensed products. If our total expenditures in any 12-month period do not meet or exceed the applicable diligence minimum, then we must pay Penn the amount of the shortfall. Under the terms of the agreement, we issued shares of our common stock to Penn and we are obligated to make milestone payments upon the achievement of certain regulatory milestones relating to the licensed products, which could, in the aggregate, reach a maximum of $5.5 million per licensed product if all milestones are achieved for such licensed product. Upon mutual agreement between Penn and us, we could elect to pay up to 100% of such amounts with shares of our common stock. In addition, we are obligated to pay Penn a mid-single-digit royalty, on a country-by-country basis, on net sales of licensed products covered by a licensed patent claim so long as the licensed product achieves and retains orphan designation, and if the licensed product does not receive or retain orphan product designation, we are obligated to pay Penn a low-single digit royalty on a country-by-country basis. We are obligated to pay Penn specified percentages of certain non-royalty payments and other consideration we may receive from any sublicense of our rights under the license agreements, with the specified percentage dependent on the timing of the sublicense grant. Penn controls the prosecution and maintenance of the licensed patent rights. We also made an initial cash payment to Penn to cover all of Penn's previously incurred patent expenses relating to the licensed patent rights. This license will expire upon the expiration or abandonment of all of the patents and patent applications subject to the license, the latest of which, if it issues as a patent, is currently expected to expire in 2032. Penn may terminate the license upon uncured material breaches by us of the terms of the license and upon the occurrence of certain events, including specified bankruptcy and insolvency events relating to us, or if we commence an action against Penn to declare or render invalid or unenforceable the patent rights. We may terminate the license at any time upon giving 60 days' prior written notice to Penn.

University of Iowa Research Foundation

In December 2013, we entered into a license agreement with UIRF, which we amended in January 2016 to expand the list of patent and patent applications to which we have rights. Under the license agreement, as amended, UIRF granted us an exclusive worldwide license, with the right to sublicense, to a portfolio of approximately 96 gene therapy patents and patent applications owned by UIRF or jointly owned by UIRF and Massachusetts General Hospital related to RNA interference and gene therapy technologies, and to the results of a certain research collaboration among UIRF, Howard Hughes Medical Institute and CHOP, to manufacture and commercialize products covered by the licensed patent rights or discovered, developed, manufactured or commercialized through the use of the research collaboration results. Under the terms of the license agreement, we are obligated to use reasonable efforts to develop and commercialize licensed products. In connection with the agreement, we issued shares of our common stock and made a cash payment of approximately $157,000 to UIRF, and we are obligated to make milestone payments upon the achievement of certain regulatory milestones relating to the licensed products, which could, in the aggregate, reach a maximum of $1.3 million if all milestones are achieved. In addition, we are obligated to pay UIRF a low-single-digit royalty on a country-by-country basis on net sales of licensed products covered by a valid licensed patent claim. Commencing in 2017, we are obligated to pay an aggregate of $40,000 in annual license maintenance fees to UIRF, which are creditable against specified milestone and royalty payment obligations accruing in the same year. The license

maintenance fees and royalty rates are subject to increase if we, or any person or entity acting on our behalf, bring any action or claim challenging the validity or enforceability of the licensed patent rights. UIRF is responsible for prosecution and maintenance of the licensed patent rights and we have agreed to reimburse UIRF for reasonable expenses incurred in prosecution and maintenance of the licensed patent rights. Upon mutual agreement between UIRF and us, we could elect to pay some or all of our payment obligations under the license with shares of our

common stock.

The license agreement and our obligation to pay royalties expire, unless earlier terminated, on a country-by-country and licensed product-by-licensed product basis, upon the expiration of the last to expire valid claim, as defined in the agreement in the licensed patent rights (including patent applications) covering the manufacture, use, sale or importation of such licensed product in such country. Following the expiration of our obligation to pay royalties on a licensed product in a country, we will retain a fully paid-up, non-royalty-bearing, perpetual license to the results of the collaboration relating to such licensed product in such country. UIRF may terminate this license or render it non-exclusive at any time after October 14, 2018 if we have both (i) not put the licensed product into commercial use in any country and (ii) are not demonstrably engaged in a program directed toward achieving commercial use of the product, and if we fail to eliminate such conditions within a specified cure period following notice from UIRF. UIRF may also terminate this license upon uncured material breaches by us of the terms of the license, subject to a specified notice and cure period. The license agreement automatically terminates if we undergo certain bankruptcy or insolvency events. We may terminate the license at any time upon giving 90 days' prior written notice to UIRF.

Table of Contents

Selecta Biosciences, Inc.

In December 2016, we entered into a license agreement that provides us with exclusive worldwide rights to Selecta's proprietary SVP™ platform technology for co-administration with gene therapy targets, including factor VIII for hemophilia A, as well as exclusive options for up to four additional undisclosed genetic targets.

Selecta's immune tolerance SVP, including SVP-Rapamycin, is an investigational technology intended to suppress the formation of neutralizing antibodies to an AAV capsid when used in combination with gene therapies, without altering the therapeutic profile of the gene therapy. Neutralizing antibodies form in response to an initial administration of an AAV gene therapy and prevent effective subsequent usage. The potential ability to re-dose a gene therapy may be beneficial where a patient has not achieved a sufficient therapeutic expression of the transferred gene in the initial dose.

Subject to the terms of the agreement, we made an initial $10.0 million cash payment to Selecta and purchased $5.0 million of Selecta's common stock. During 2017, we paid Selecta an additional $5.0 million in cash and purchased an additional $10.0 million of Selecta's common stock. Selecta will be eligible for up to $430.0 million in milestone payments for each target, with up to $65.0 million being based on our achievement of specified development and regulatory milestones and up to $365.0 million for specified commercial milestones. In addition, we will pay Selecta tiered mid-single to low-double-digit royalties on worldwide annual net sales of any resulting commercialized gene therapy.

Competition

The biotechnology and pharmaceutical industries, including the gene therapy field, are characterized by rapidly changing technologies, significant competition and a strong emphasis on intellectual property. We face substantial competition from many different sources, including large and specialty pharmaceutical and biotechnology companies, academic research institutions, government agencies and public and private research institutions.

We are aware of companies focused on developing AAV gene therapies in various indications, including 4D Molecular Therapeutics, Abeona Therapeutics Inc., Actus Therapeutics, Inc., Adverum Biotechnologies, Inc., Amicus Therapeutics, Inc., Applied Genetic Technologies Corporation, Asklepios BioPharmaceutical, Inc., Audentes Therapeutics, Inc., Axovant Sciences, Inc., BioMarin Pharmaceutical Inc., GenSight Biologics SA, Homology Medicines, Inc., Horama SAS, Lysogene SAS, MeiraGTx Limited, Nightstar Therapeutics plc, PTC Therapeutics, Inc., REGENXBIO, Inc., Sangamo Therapeutics, Inc., Sarepta Therapeutics, Inc., Solid Biosciences, Inc., Ultragenyx Pharmaceuticals, Inc., uniQure N.V. and Voyager Therapeutics, Inc., as well as several companies addressing other methods for delivering or modifying genes and regulating gene expression. Any advances in gene therapy technology made by a competitor may be used to develop therapies that could compete against LUXTURNA and any of our product candidates.

For LUXTURNA and clinical product candidates we have developed, the main competitors include:

- **LUXTURNA**. While no other approved pharmacologic agents exist for patients with *RPE65*-mediated IRD, Second Sight Medical Products, Inc. has received approval from FDA and other foreign regulatory authorities for a retinal prosthesis medical device, which is being marketed to RP patients with limited or no light perception. Another retinal prosthesis medical device from Retina Implant AG has obtained a CE Certificate of Conformity from its notified body, and is similarly indicated for blinded patients. Novelion Therapeutics, Inc. (formerly QLT Inc.) completed a Phase 1b clinical trial of a vitamin A derivative to treat RP and LCA. In the gene therapy space, certain companies and several academic institutions have conducted or plan to conduct clinical trials involving *RPE65*-based product candidates, including MeiraGTx Limited and Horama SAS. To date, none of these organizations has completed a trial involving injection of a subject’s second eye or has initiated a Phase 3 trial.

- ***SPK-CHM***. We are aware that Nightstar Therapeutics plc, or Nightstar, is developing an AAV-based gene therapy for the treatment of choroideremia. Nightstar has obtained orphan product designation in the United States and the European Union for this product candidate for the treatment of choroideremia and has announced that it has initiated a Phase 3 trial for choroideremia. We are also aware that 4D Molecular Therapeutics and F. Hoffmann-La Roche AG have pre-clinical programs in process.

SPK-FVIII. The standard of care for moderate to severe hemophilia A patients is intravenously administered factor VIII protein or its derivatives that are produced by several companies. There are other companies developing gene therapies to treat hemophilia A, including BioMarin Pharmaceutical Inc., Ultragenyx Pharmaceuticals, Inc., in collaboration with Bayer HealthCare, Shire PLC, uniQure N.V., Sangamo Therapeutics, Inc. in collaboration with Pfizer and Telethon Institute for Gene Therapy in collaboration with Sanofi.

- Many of our potential competitors, alone or with their strategic partners, have substantially greater financial, technical and other resources, such as larger research and development, clinical, marketing and manufacturing organizations. Mergers and

Table of Contents

acquisitions in the biotechnology and pharmaceutical industries may result in even more resources being concentrated among a smaller number of competitors. Our commercial opportunity could be reduced or eliminated if competitors develop and commercialize products that are safer, more effective, have fewer or less severe side effects, are more convenient or are less expensive than any products that we may develop. Competitors also may obtain FDA or other regulatory approval for their products more rapidly or earlier than we may obtain approval for ours, which could result in our competitors establishing a strong market position before we are able to enter the market. Additionally, technologies developed by our competitors may render our product or product candidates uneconomical or obsolete, and we may not be successful in marketing our product or product candidates against competitors.

Regulation of gene therapies

In the United States, FDA regulates biologic products including gene therapy products under the Federal Food, Drug, and Cosmetic Act, or FDCA, and the Public Health Service Act, or PHSA. The FDCA, PHSA and their implementing regulations govern, among other things, the testing, manufacturing, safety, efficacy, labeling, packaging, storage, record keeping, distribution, advertising and promotion of biologic products. Before conducting human studies with an investigational gene therapy, the sponsor must notify the FDA through the Investigational New Drug application process. Upon completion of clinical studies, the sponsor submits a Biologics License Application or BLA, to FDA, which then determines whether the product should be approved for marketing.

Within FDA, the Center for Biologics Evaluation and Research, or CBER, regulates gene therapy products. Within CBER, the review of gene therapy and related products is consolidated in the Office of Cellular, Tissue and Gene Therapies, or OCTGT, and FDA has established the Cellular, Tissue and Gene Therapies Advisory Committee, or CTGTAC, a panel of medical and scientific experts and consumer representatives, to advise CBER on its reviews. CBER works closely with NIH and the Regulatory Affairs Certification, or RAC, which makes recommendations to NIH on gene therapy issues and engages in a public discussion of scientific, safety, ethical and societal issues related to gene therapies and their development. FDA has issued a growing body of guidance documents on chemistry, manufacturing and control, or CMC, clinical investigations and other areas of gene therapy development, all of which are intended to facilitate the industry's development of gene therapy products.

U.S. biologic products development process

The process required by FDA before a biologic product candidate may be marketed in the United States generally involves the following:

- completion of preclinical laboratory tests and *in vivo* studies in accordance with FDA's current Good Laboratory Practice, or GLP, regulations and applicable requirements for the humane use of laboratory animals or other applicable regulations;
- submission to FDA of an application for an IND exemption, which allows human clinical trials to begin unless FDA objects within 30 days;
- approval by an independent institutional review board, or IRB, reviewing each clinical site before each clinical trial may be initiated;
- performance of adequate and well-controlled human clinical trials according to FDA's Good Clinical Practice, or GCP, regulations, and any additional requirements for the protection of human research subjects and their health information, to establish the safety and efficacy of the proposed biologic product candidate for its intended use;
- preparation and submission to FDA of a BLA for marketing approval that includes substantial evidence of safety, purity and potency from results of animal and laboratory testing and clinical trials;
- satisfactory completion of an FDA inspection of the manufacturing facility or facilities where the biologic product candidate is produced to assess compliance with cGMP and to assure that the facilities, methods and controls are adequate to preserve the biologic product candidate's identity, safety, strength, quality, potency and purity;

- potential FDA audit of the nonclinical and clinical trial sites that generated the data in support of the BLA; and
- payment of user fees and FDA review and approval, or licensure, of the BLA. BLA or new drug application, or NDA, application fees for products designated as orphan drugs by FDA are waived.

Table of Contents

Before testing any biologic product candidate in humans, including a gene therapy product candidate, the product candidate must undergo preclinical testing. Preclinical tests, also referred to as nonclinical studies, include laboratory evaluations of product chemistry, toxicity and formulation, as well as *in vivo* studies to assess the potential safety and activity of the product candidate. The conduct of the preclinical tests must comply with federal regulations and requirements including GLPs.

If a gene therapy trial is conducted at, or sponsored by, institutions receiving NIH funding for recombinant DNA research, prior to the submission of an IND to FDA, a protocol and related documents must be submitted to, and the study registered with, the NIH Office of Biotechnology Activities, or OBA, pursuant to the NIH Guidelines for Research Involving Recombinant DNA Molecules, or NIH Guidelines. Compliance with the NIH Guidelines is mandatory for investigators at institutions receiving NIH funds for research involving recombinant DNA. However, many companies and other institutions, not otherwise subject to the NIH Guidelines, voluntarily follow them. NIH is responsible for convening the RAC that discusses protocols that raise novel or particularly important scientific, safety or ethical considerations at one of its quarterly public meetings. The OBA will notify FDA of the RAC's decision regarding the necessity for full public review of a gene therapy protocol. RAC proceedings and reports are posted to the OBA website and may be accessed by the public.

The clinical trial sponsor must submit the results of the preclinical tests, together with manufacturing information, analytical data, any available clinical data or literature and a proposed clinical protocol, to FDA as part of the IND. Some preclinical testing may continue even after the IND is submitted. The IND automatically becomes effective 30 days after receipt by FDA, unless FDA places the clinical trial on a clinical hold. In such a case, the IND sponsor and FDA must resolve any outstanding concerns before the clinical trial can begin. With gene therapy protocols, if FDA allows the IND to proceed, but the RAC decides that full public review of the protocol is warranted, FDA will request at the completion of its IND review that sponsors delay initiation of the protocol until after completion of the RAC review process. FDA also may impose clinical holds on a biologic product candidate at any time before or during clinical trials due to safety concerns or non-compliance. If FDA imposes a clinical hold, trials may not recommence without FDA authorization and then only under terms authorized by FDA.

Human clinical trials under an IND

Clinical trials involve the administration of the biologic product candidate to healthy volunteers or patients under the supervision of qualified investigators which generally are physicians not employed by, or under, the control of the trial sponsor. Clinical trials are conducted under protocols detailing, among other things, the objectives of the clinical trial, dosing procedures, subject selection and exclusion criteria and the parameters to be used to monitor subject safety, including stopping rules that assure a clinical trial will be stopped if certain adverse events should occur. Each protocol and any amendments to the protocol must be submitted to FDA as part of the IND. Clinical trials must be conducted and monitored in accordance with FDA's regulations comprising the GCP requirements, including the requirement that all research subjects provide informed consent.

Further, each clinical trial must be reviewed and approved by an IRB at or servicing each institution at which the clinical trial will be conducted. An IRB is charged with protecting the welfare and rights of trial participants and considers items such as whether the risks to individuals participating in the clinical trials are minimized and are reasonable in relation to anticipated benefits. The IRB also approves the form and content of the informed consent that must be signed by each clinical trial subject, or his or her legal representative, and must monitor the clinical trial until completed. Clinical trials involving recombinant DNA also must be reviewed by an institutional biosafety committee, or IBC, a local institutional committee that reviews and oversees basic and clinical research that utilizes recombinant DNA at that institution. The IBC assesses the safety of the research and identifies any potential risk to public health or the environment.

Human clinical trials typically are conducted in three sequential phases that may overlap or be combined:

- *Phase 1*. The biologic product candidate initially is introduced into healthy human subjects and tested for safety, dosage tolerance, absorption, metabolism, distribution, excretion and, if possible, to gain an early understanding of its effectiveness. In the case of some product candidates for severe or life-threatening diseases, especially when the product candidate may be too inherently toxic to ethically administer to healthy volunteers, the initial human testing is

often conducted in patients.

- *Phase 2*. The biologic product candidate is evaluated in a limited patient population to identify possible adverse effects and safety risks, to preliminarily evaluate the efficacy of the product candidate for specific targeted diseases and to determine dosage tolerance, optimal dosage and dosing schedule.

- *Phase 3*. The biologic product candidate is administered to an expanded patient population at geographically dispersed clinical trial sites in adequate and well-controlled clinical trials to generate sufficient data to statistically

Table of Contents

confirm the potency and safety of the product for approval. These clinical trials are intended to establish the overall risk/benefit ratio of the product candidate and provide an adequate basis for product labeling.

Post-approval clinical trials, sometimes referred to as Phase 4 clinical trials, may be conducted after initial approval. These clinical trials are used to gain additional experience from the treatment of patients in the intended therapeutic indication, particularly for long-term safety follow-up.

During all phases of clinical development, regulatory agencies require extensive monitoring and auditing of all clinical activities, clinical data and clinical trial investigators. Annual progress reports detailing the results of the clinical trials must be submitted to FDA.

Written IND safety reports must be promptly submitted to FDA, NIH and the investigators for: serious and unexpected adverse events; any findings from other trials, *in vivo* laboratory tests or *in vitro* testing that suggest a significant risk for human subjects; or any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure. The sponsor must submit an IND safety report within 15 calendar days after the sponsor determines that the information qualifies for reporting. The sponsor also must notify FDA of any unexpected fatal or life-threatening suspected adverse reaction within seven calendar days after the sponsor's initial receipt of the information.

FDA or the sponsor or its data safety monitoring board may suspend a clinical trial at any time on various grounds, including a finding that the research subjects or patients are being exposed to an unacceptable health risk. Similarly, an IRB can suspend or terminate approval of a clinical trial at its institution if the clinical trial is not being conducted in accordance with the IRB's requirements or if the biologic product candidate has been associated with unexpected serious harm to patients.

Additional regulation for gene therapy clinical trials

In addition to the regulations discussed above, there are a number of additional standards that apply to clinical trials involving gene therapies. FDA has issued various guidance documents regarding gene therapies, which outline additional factors that FDA will consider at each of the above stages of development and relate to, among other things: the proper preclinical assessment of gene therapies; the CMC information that should be included in an IND application; the proper design of tests to measure product potency in support of an IND or BLA application; and measures to observe delayed adverse effects in subjects who have been exposed to investigational gene therapies when the risk of such effects is high. Further, FDA usually recommends that sponsors observe subjects for potential gene therapy-related delayed adverse events for a 15-year period, including a minimum of five years of annual examinations followed by 10 years of annual queries, either in person or by questionnaire.

NIH and FDA have a publicly accessible database, the Genetic Modification Clinical Research Information System, which includes information on gene therapy trials and serves as an electronic tool to facilitate the reporting and analysis of adverse events on these trials.

Compliance with cGMP requirements

Manufacturers of biologics must comply with applicable cGMP regulations, including quality control and quality assurance and maintenance of records and documentation. Manufacturers and others involved in the manufacture and distribution of such products also must register their establishments with FDA and certain state agencies. Sites in the United States that manufacture products intended to be distributed in the EU are subject to inspections by the competent authority in the importing EU country to ensure compliance with cGMP. Both domestic and foreign manufacturing establishments must register and provide additional information to FDA and the EMA upon their initial participation in the manufacturing process. Establishments may be subject to periodic, unannounced inspections by government authorities to ensure compliance with cGMP requirements and other laws. Discovery of problems may result in a government entity placing restrictions on a product, manufacturer or holder of an approved BLA, and may extend to requiring withdrawal of the product from the market. Neither FDA nor the EMA will approve an application unless it determines that the manufacturing processes and facilities comply with cGMP requirements and adequate to assure consistent production of the product within required specification.

Concurrent with clinical trials, companies usually complete additional preclinical studies and must also develop additional information about the physical characteristics of the biologic product candidate as well as finalize a process for manufacturing the product candidate in commercial quantities in accordance with cGMP requirements. To help

reduce the risk of the introduction of adventitious agents or of causing other adverse events with the use of biologic products, the PHSA emphasizes the importance of manufacturing control for products whose attributes cannot be precisely defined. The manufacturing process must be capable of consistently producing quality batches of the product candidate and, among other requirements, the sponsor must develop methods for testing the identity, strength, quality, potency and purity of the final biologic product. Additionally, appropriate packaging must be selected and tested and stability studies must be conducted to demonstrate that the biologic product candidate does not undergo unacceptable deterioration over its shelf life.

Table of Contents

U.S. review and approval processes

The results of the preclinical tests and clinical trials, together with detailed information relating to the product's CMC and proposed labeling, among other things, are submitted to FDA as part of a BLA requesting approval to market the product for one or more indications.

For gene therapies, selecting patients with applicable genetic defects is a necessary condition to effective treatment. For the therapies we are currently developing, we believe that diagnoses based on symptoms, in conjunction with existing genetic tests developed and administered by laboratories certified under the Clinical Laboratory Improvement Amendments, or CLIA, are sufficient to select appropriate patients and will be permitted by FDA. For future therapies, however, it may be necessary to use FDA-cleared or FDA-approved diagnostic tests to select patients or to assure the safe and effective use of therapies in appropriate patients. FDA refers to such tests as *in vitro* companion diagnostic devices. On July 31, 2014, FDA announced the publication of a final guidance document describing the agency's current thinking about the development and regulation of *in vitro* companion diagnostic devices. The final guidance articulates a policy position that, when safe and effective use of a therapeutic product depends on a diagnostic device, FDA generally will require approval or clearance of the diagnostic device at the same time that FDA approves the therapeutic product. The final guidance allows for two exceptions to the general rule of concurrent drug/device approval, namely, when the therapeutic product is intended to treat serious and life-threatening conditions for which no alternative exists, and when a serious safety issue arises for an approved therapeutic agent, and no FDA-cleared or FDA-approved companion diagnostic test is yet available. At this point, it is unclear how FDA will apply this policy to our future gene therapy candidates, or even to our current products. Should FDA deem genetic tests used for selecting appropriate patients for our therapies to be *in vitro* companion diagnostics requiring FDA clearance or approval, we may face significant delays or obstacles in obtaining approval for a BLA.

In addition, under the Pediatric Research Equity Act, or PREA, a BLA or supplement to a BLA must contain data to assess the safety and effectiveness of the biologic product candidate for the claimed indications in all relevant pediatric subpopulations and to support dosing and administration for each pediatric subpopulation for which the product candidate is safe and effective. FDA may grant deferrals for submission of data or full or partial waivers. Unless otherwise required by regulation, PREA does not apply to any biologic product candidate for an indication for which orphan designation has been granted.

Under the Prescription Drug User Fee Act, or PDUFA, as amended, each BLA must be accompanied by a user fee. FDA adjusts the PDUFA user fees on an annual basis. According to FDA's fee schedule, effective through September 30, 2016, the user fee for an application requiring clinical data, such as a BLA, is $2,374,200. PDUFA also imposes an annual product fee for biologics ($114,450) and an annual establishment license fee ($585,200) on facilities used to manufacture prescription biologics. Fee waivers or reductions are available in certain circumstances, including a waiver of the application fee for the first application filed by a small business. Additionally, no user fees are assessed on BLAs for product candidates designated as orphan drugs, unless the product candidate also includes a non-orphan indication.

FDA reviews a BLA within 60 days of submission to determine if it is substantially complete before the agency accepts it for filing. FDA may refuse to file any BLA that it deems incomplete or not properly reviewable at the time of submission and may request additional information. In that event, the BLA must be resubmitted with the additional information. The resubmitted application also is subject to review before FDA accepts it for filing. Once the submission is accepted for filing, FDA begins an in-depth, substantive review of the BLA.

FDA reviews the BLA to determine, among other things, whether the proposed product candidate is safe and potent, or effective, for its intended use, has an acceptable purity profile and whether the product candidate is being manufactured in accordance with cGMP to assure and preserve the product candidate's identity, safety, strength, quality, potency and purity. FDA may refer applications for novel biologic products or biologic products that present difficult questions of safety or efficacy to an advisory committee, typically a panel that includes clinicians and other experts, for review, evaluation and a recommendation as to whether the application should be approved and under what conditions. FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions. During the product approval process, FDA also will determine whether a risk evaluation and mitigation strategy, or REMS, is necessary to assure the safe use of the product

candidate. A REMS could include medication guides, physician communication plans and elements to assure safe use, such as restricted distribution methods, patient registries and other risk minimization tools. If FDA concludes a REMS is needed, the sponsor of the BLA must submit a proposed REMS; FDA will not approve the BLA without a REMS, if required.

Before approving a BLA, FDA will inspect the facilities at which the product candidate is manufactured. FDA will not approve the product candidate unless it determines that the manufacturing processes and facilities comply with cGMP requirements and adequate to assure consistent production of the product candidate within required specifications. Additionally, before approving a BLA, FDA typically will inspect one or more clinical sites to assure that the clinical trials were conducted in compliance with IND trial requirements and GCP requirements.

Table of Contents

Upon completion of its review of the BLA, FDA may issue an approval letter or a complete response letter. An approval letter authorizes commercial marketing of the biologic product with specific prescribing information for specific indications. The approval letter also may impose certain conditions of approval, such as a REMS. A complete response letter generally outlines the deficiencies in the application and may require the sponsor to undertake substantial additional testing or provide additional information for FDA to reconsider the application. If those deficiencies have been addressed to FDA's satisfaction in a resubmission of the BLA, FDA will issue an approval letter.

If a product candidate receives regulatory approval, the approval may be significantly limited to specific diseases and dosages or the indications for use may otherwise be limited. Further, FDA may require that certain contraindications, warnings or precautions be included in the product labeling. FDA may impose restrictions and conditions on product distribution, prescribing or dispensing in the form of a REMS, or otherwise limit the scope of any approval. In addition, FDA may require post-marketing clinical trials, sometimes referred to as Phase 4 clinical trials, designed to further assess a biologic product's safety and effectiveness, and testing and surveillance programs to monitor the safety of approved products that have been commercialized.

FDA has agreed to specified performance goals in the review of BLAs under the PDUFA. One such goal is to review 90% of standard BLAs in 10 months after FDA accepts the BLA for filing, and 90% of priority BLAs in six months, whereupon a review decision is to be made. The FDA does not always meet its PDUFA goal dates for standard and priority BLAs and its review goals are subject to change from time to time. The review process and the PDUFA goal date may be extended by three months if the FDA requests or the BLA sponsor otherwise provides additional information or clarification regarding information already provided in the submission within the last three months before the PDUFA goal date.

Orphan drug designation

Under the Orphan Drug Act, FDA may designate a biologic product as an "orphan drug" if it is intended to treat a rare disease or condition (generally meaning that it affects fewer than 200,000 individuals in the United States, or more in cases in which there is no reasonable expectation that the cost of developing and making a biologic product available in the United States for treatment of the disease or condition will be recovered from sales of the product). Orphan product designation must be requested before submitting a BLA. After FDA grants orphan product designation, the identity of the therapeutic agent and its potential orphan use are disclosed publicly by FDA. Orphan product designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process.

If a product with orphan status receives the first FDA approval for the disease or condition for which it has such designation, the product is entitled to orphan product exclusivity, meaning that FDA may not approve any other applications to market the same drug or biologic product for the same indication for seven years, except in limited circumstances, such as a showing of clinical superiority to the product with orphan exclusivity or if the party holding the exclusivity fails to assure the availability of sufficient quantities of the drug to meet the needs of patients with the disease or condition for which the drug was designated. Competitors, however, may receive approval of different products for the same indication for which the orphan product has exclusivity or obtain approval for the same product but for a different indication for which the orphan product has exclusivity. Orphan medicinal product status in the European Union has similar, but not identical, benefits.

Expedited development and review programs

FDA is authorized to expedite the review of BLAs in several ways. Under the Fast Track program, the sponsor of a biologic product candidate may request FDA to designate the product for a specific indication as a Fast Track product concurrent with or after the filing of the IND. Biologic products are eligible for Fast Track designation if they are intended to treat a serious or life-threatening condition and demonstrate the potential to address unmet medical needs for the condition. Fast Track designation applies to the combination of the product candidate and the specific indication for which it is being studied. In addition to other benefits, such as the ability to have greater interactions with FDA, FDA may initiate review of sections of a Fast Track BLA before the application is complete, a process known as rolling review.

Any product submitted to FDA for marketing, including under a Fast Track program, may be eligible for other types of FDA programs intended to expedite development and review, such as breakthrough therapy designation, priority

review and accelerated approval.

Breakthrough therapy designation. To qualify for the breakthrough therapy program, product candidates must be intended to treat a serious or life-threatening disease or condition and preliminary clinical evidence must indicate that such product candidates may demonstrate substantial improvement on one or more clinically significant endpoints over existing therapies. FDA will seek to ensure the sponsor of a breakthrough therapy product candidate receives: intensive guidance on an efficient drug development program; intensive involvement of senior managers and experienced staff on a proactive, collaborative and cross-disciplinary review; and rolling review.

Table of Contents

- *Priority review*. A product candidate is eligible for priority review if it treats a serious condition and, if approved, it would be a significant improvement in the safety or effectiveness of the treatment, diagnosis or prevention of a serious condition compared to marketed products. FDA aims to complete its review of priority review applications within six months as opposed to 10 months for standard review.

Accelerated approval. Drug or biologic products studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit over existing treatments may receive accelerated approval. Accelerated approval means that a product candidate may be approved on the basis of adequate and well-controlled clinical trials establishing that the product candidate has an effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit, or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity and prevalence of the condition and the availability or lack of alternative treatments. As a condition of approval, FDA may require that a sponsor of a drug or biologic product candidate receiving accelerated approval perform adequate and well-controlled post-marketing clinical trials. In addition, FDA currently requires as a condition for accelerated approval pre-approval of promotional materials.

Fast Track designation, breakthrough therapy designation, priority review and accelerated approval do not change the standards for approval but may expedite the development or approval process.

Finally, with passage of the 21st Century Cures Act, or the Cures Act, in December 2016, Congress authorized FDA to accelerate review and approval of products designated as regenerative advanced therapies. A product is eligible for this designation if it is a regenerative medicine therapy (which may include a cell therapy) that is intended to treat, modify, reverse or cure a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the drug has the potential to address unmet medical needs for such disease or condition. The benefits of a regenerative advanced therapy designation include early interactions with FDA to expedite development and review, benefits available to breakthrough therapies, potential eligibility for priority review and accelerated approval based on surrogate or intermediate endpoints.

Post-approval requirements

Rigorous and extensive FDA regulation of biologic products continues after approval, particularly with respect to cGMP requirements. Manufacturers are required to comply with applicable requirements in the cGMP regulations, including quality control and quality assurance and maintenance of records and documentation. Other post-approval requirements applicable to biologic products include reporting of cGMP deviations that may affect the identity, potency, purity and overall safety of a distributed product, record-keeping requirements, reporting of adverse effects, reporting updated safety and efficacy information and complying with electronic record and signature requirements. After a BLA is approved, the product also may be subject to official lot release. If the product is subject to official release by FDA, the manufacturer submits samples of each lot of product to FDA, together with a release protocol, showing a summary of the history of manufacture of the lot and the results of all tests performed on the lot. FDA also may perform certain confirmatory tests on lots of some products before releasing the lots for distribution. In addition, FDA conducts laboratory research related to the regulatory standards on the safety, purity, potency and effectiveness of biologic products.

A sponsor also must comply with FDA's advertising and promotion requirements, such as those related to direct-to-consumer advertising, the prohibition on promoting products for uses or in patient populations that are not described in the product's approved labeling (known as "off-label use"). Discovery of previously unknown problems or the failure to comply with the applicable regulatory requirements may result in restrictions on the marketing of a product or withdrawal of the product from the market as well as possible civil or criminal sanctions. In addition, changes to the manufacturing process or facility generally require prior FDA approval before being implemented and other types of changes to the approved product, such as adding new indications and additional labeling claims, are also subject to further FDA review and approval.

Failure to comply with the applicable U.S. requirements at any time during the product development process, approval process or after approval, may subject an applicant or manufacturer to administrative or judicial civil or criminal actions and adverse publicity. These actions could include refusal to approve pending applications or supplemental

applications, withdrawal of an approval, clinical hold, suspension or termination of clinical trial by an IRB, warning or untitled letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines or other monetary penalties, refusals of government contracts, mandated corrective advertising or communications to healthcare professionals or patients, debarment, restitution, disgorgement of profits or other civil or criminal penalties.

U.S. patent term restoration and marketing exclusivity

Depending upon the timing, duration and specifics of FDA approval of product candidates, some of a sponsor's U.S. patents may be eligible for limited patent term extension under the Drug Price Competition and Patent Term Restoration Act of 1984. The Hatch-Waxman Amendments permit a patent restoration term of up to five years as compensation for patent term lost

Table of Contents

during product development and FDA regulatory review process. However, patent term restoration cannot extend the remaining term of a patent beyond a total of 14 years from the product's approval date. The patent term restoration period generally is one-half the time between the effective date of an IND and the submission date of a BLA plus the time between the submission date of a BLA and the approval of that application. Only one patent applicable to an approved biologic product is eligible for the extension and the application for the extension must be submitted prior to the expiration of the patent. The United States Patent and Trademark Office, or USPTO, in consultation with FDA, reviews and approves the application for any patent term extension or restoration.

Pediatric exclusivity

Pediatric exclusivity is a type of non-patent marketing exclusivity in the United States that, if granted, provides for the attachment of an additional six months of marketing protection to the term of any existing regulatory exclusivity, including the non-patent and orphan exclusivity. This six-month exclusivity may be granted if a BLA sponsor submits pediatric data that fairly respond to a written request from FDA for such data. The data do not need to show the product to be effective in the pediatric population studied; rather, if the clinical trial is deemed to fairly respond to FDA's request, the additional protection is granted. If reports of requested pediatric studies are submitted to, and accepted by, FDA within the statutory time limits, whatever statutory or regulatory periods of exclusivity or patent protection that cover the product are extended by six months. This is not a patent term extension, but it effectively extends the regulatory period during which FDA cannot accept or approve a biosimilar application.

Biosimilars and exclusivity

The Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, or PPACA, created an abbreviated approval pathway for biologic products shown to be similar to, or interchangeable with, an FDA-licensed reference biologic product, referred to as biosimilars. For FDA to approve a biosimilar product, it must find that there are no clinically meaningful differences between the reference product and proposed biosimilar product. Interchangeability requires that a product is biosimilar to the reference product and the product must demonstrate that it can be expected to produce the same clinical results as the reference product and, for products administered multiple times, the biologic and the reference biologic may be switched after one has been previously administered without increasing safety risks or risks of diminished efficacy relative to exclusive use of the reference biologic.

A reference biologic is granted 12 years of exclusivity from the time of first licensure of the reference product. An application for a biosimilar product may not be submitted to FDA until four years following approval of the reference product, and it may not be approved until 12 years thereafter. These exclusivity provisions only apply to biosimilars—companies that rely on their own data and file a full BLA may be approved earlier than 12 years. As an innovator, we plan to file a full BLA to support market approval of all of our current and future products.

The 21st Century Cures Act

On December 13, 2016, President Obama signed the Cures Act into law. The Cures Act is designed to modernize and personalize healthcare, spur innovation and research and streamline the discovery and development of new therapies through increased federal funding of particular programs. It authorizes increasing funding for FDA to spend on innovation projects. The new law also amends the Public Health Service Act to reauthorize and expand funding for the NIH. The Cures Act establishes the NIH Innovation Fund to pay for the cost of development and implementation of a strategic plan, early stage investigators and research. It also charges NIH with leading and coordinating expanded pediatric research. Further, the Cures Act directs the Centers for Disease Control and Prevention to expand surveillance of neurological diseases.

With amendments to the FDCA and the Public Health Service Act, or PHSA, Title III of the Cures Act seeks to accelerate the discovery, development and delivery of new medicines and medical technologies. To that end, and among other provisions, the Cures Act reauthorizes for four years the priority review voucher program for certain

drugs intended to treat rare pediatric diseases; creates a new priority review voucher program for drug applications determined to be material threat medical countermeasure applications; revises the FDCA to streamline review of combination product applications; requires FDA to evaluate the potential use of "real world evidence" to help support approval of new indications for approved drugs; provides a new "limited population" approval pathway for antibiotic and antifungal drugs intended to treat serious or life-threatening infections; and authorizes FDA to designate a drug as a "regenerative advanced therapy," thereby making it eligible for certain expedited review and approval designations.

FDA approval of companion diagnostics

Table of Contents

In August 2014, the FDA issued final guidance clarifying the requirements that will apply to approval of therapeutic products and *in vitro* companion diagnostics. According to the guidance, for novel drugs, a companion diagnostic device and its corresponding therapeutic should be approved or cleared contemporaneously by FDA for the use indicated in the therapeutic product's labeling. Approval or clearance of the companion diagnostic device will ensure that the device has been adequately evaluated and has adequate performance characteristics in the intended population. Under the FDCA, *in vitro* diagnostics, including companion diagnostics, are regulated as medical devices. In the United States, the FDCA and its implementing regulations, and other federal and state statutes and regulations govern, among other things, medical device design and development, preclinical and clinical testing, premarket clearance or approval, registration and listing, manufacturing, labeling, storage, advertising and promotion, sales and distribution, export and import and post market surveillance. Unless an exemption applies, diagnostic tests require marketing clearance or approval from the FDA prior to commercial distribution. FDA has not indicated that it would require a companion diagnostic with LUXTURNA.

Government regulation outside of the United States

In addition to regulations in the United States, sponsors are subject to a variety of regulations in other jurisdictions governing, among other things, clinical trials and any commercial sales and distribution of biologic products. Because biologically sourced raw materials are subject to unique contamination risks, their use may be restricted in some countries.

Whether or not a sponsor obtains FDA approval for a product, a sponsor must obtain the requisite approvals from regulatory authorities in foreign countries prior to the commencement of clinical trials or marketing of the product in those countries. Certain countries outside of the United States have a similar process that requires the submission of a clinical trial application, much like the IND, prior to the commencement of human clinical trials. In the European Union, for example, a request for a Clinical Trial Authorization, or CTA, must be submitted to the competent regulatory authorities and the competent Ethics Committees in the European Union Member States in which the clinical trial takes place, much like FDA and the IRB, respectively. Once the CTA request is approved in accordance with the European Union and the European Union Member State's requirements, clinical trial development may proceed.

The requirements and processes governing the conduct of clinical trials, product licensing, pricing and reimbursement vary from country to country. In all cases, the clinical trials are conducted in accordance with GCPs and the applicable regulatory requirements and the ethical principles that have their origin in the Declaration of Helsinki.

Failure to comply with applicable foreign regulatory requirements may result in, among other things, fines, suspension, variation or withdrawal of regulatory approvals, product recalls, seizure of products, operating restrictions and criminal prosecution.

European Union regulation and exclusivity

To obtain regulatory approval of an investigational biologic product under European Union regulatory systems, applicants must submit a marketing authorization application, or MAA. The grant of marketing authorization in the European Union for products containing viable human tissues or cells such as gene therapy medicinal products is governed by Regulation 1394/2007/EC on advanced therapy medicinal products, read in combination with Directive 2001/83/EC of the European Parliament and of the Council, commonly known as the Community code on medicinal products. Regulation 1394/2007/EC lays down specific rules concerning the authorization, supervision and pharmacovigilance of gene therapy medicinal products, somatic cell therapy medicinal products and tissue engineered products. Manufacturers of advanced therapy medicinal products must demonstrate the quality, safety and efficacy of their products to EMA which provides an opinion regarding the application for marketing authorization. European Commission grants or refuses marketing authorization informed by the opinion delivered by EMA.

Innovative medicinal products are authorized in the European Union based on a full MAA (as opposed to an application for marketing authorization that relies on data in the marketing authorization dossier for another, previously approved medicinal product). Applications for marketing authorization for innovative medicinal products must contain the results of pharmaceutical tests, preclinical tests and clinical trials conducted with the medicinal product for which marketing authorization is sought. Innovative medicinal products for which marketing authorization is granted are entitled to eight years of data exclusivity. During this period, applicants for approval of generics or

biosimilars of these innovative products cannot rely on data contained in the marketing authorization dossier submitted for the innovative medicinal product to support their application. Innovative medicinal products for which marketing authorization is granted are also entitled to 10 years of market exclusivity. During these 10 years of market exclusivity, no generic or biosimilar medicinal product may be placed on the European Union market even if a generic or biosimilar marketing authorization can be submitted to the competent regulatory authorities in the European Union Member States. The overall 10-year period will be extended to a maximum of 11 years if, during the first eight years of those 10 years, the marketing authorization holder obtains an authorization for one or more new therapeutic indications which, during the scientific evaluation prior to their authorization, are held to bring a significant clinical benefit in comparison with existing therapies. Even if a compound is considered to be a new chemical entity and the innovator is able to gain the period of

Table of Contents

data exclusivity, another company, nevertheless, could also market another competing medicinal product for the same therapeutic indication if such company obtained marketing authorization based on an MAA with a complete independent data package of pharmaceutical tests, preclinical tests and clinical trials.

Products receiving orphan designation in the European Union can receive 10 years of market exclusivity. During this 10-year period, the competent authorities of the European Union Member States and European Commission may not accept applications or grant marketing authorization for other similar medicinal product for the same orphan indication. There are, however, three exceptions to this principle. Marketing authorization may be granted to a similar medicinal product for the same orphan indication if:

- The second applicant can establish in its application that its medicinal product, although similar to the orphan medicinal product already authorized, is safer, more effective or otherwise clinically superior;

- The holder of the marketing authorization for the original orphan medicinal product consents to a second orphan medicinal product application; or

- The holder of the marketing authorization for the original orphan medicinal product cannot supply sufficient quantities of orphan medicinal product.

An orphan product can also obtain an additional two years of market exclusivity in the European Union for the conduct of pediatric trials. The 10-year market exclusivity may be reduced to six years if, at the end of the fifth year, it is established that the product no longer meets the criteria for orphan designation; for example, if the product is sufficiently profitable not to justify maintenance of market exclusivity.

The criteria for designating an “orphan medicinal product” in the European Union are similar, in principle, to those in the United States. Orphan medicinal products are eligible for financial incentives such as reduction of fees or fee waivers. The application for orphan medicinal product designation must be submitted before the application for marketing authorization. Orphan medicinal product designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process.

In April 2014, the EU adopted a new Clinical Trials Regulation (EU) No 536/2014, or the Clinical Trials Regulation, which is set to replace the current Clinical Trials Directive 2001/20/EC, or the Clinical Trials Directive. The new Clinical Trials Regulation will become applicable no earlier than October 2018. Until the Clinical Trials Regulation will become applicable, all clinical trials performed in the European Union are required to be conducted in accordance with the Clinical Trials Directive, which will be repealed on the day of entry into application of the Clinical Trials Regulation. It will however still apply three years from that day to (i) clinical trials applications submitted before the entry into application and (ii) clinical trials applications submitted within one year after the entry into application if the sponsor opted for old system. The Clinical Trials Regulation will overhaul the current system of approvals for clinical trials in the EU. Specifically, the legislation, which will be directly applicable in all member states, aims at simplifying and streamlining the approval of clinical trials in the EU. For instance, the legislation provides for a streamlined application procedure via a single-entry point and strictly defined deadlines for the assessment of clinical trial applications.

Other healthcare laws and regulations

Healthcare professionals, physicians and third-party payers play a primary role in the recommendation and use of pharmaceutical products that are granted marketing approval. Arrangements with third-party payers, existing or potential customers and referral sources are subject to broadly applicable fraud and abuse and other healthcare laws and regulations, and these laws and regulations may constrain the business or financial arrangements and relationships through which manufacturers market, sell and distribute the products for which they obtain marketing approval. Such restrictions under applicable federal and state healthcare laws and regulations include the following:

- the federal Anti-Kickback Statute, which prohibits, among other things, persons from knowingly and willfully soliciting, receiving, offering or paying remuneration, directly or indirectly, in cash or in kind, in exchange for, or to

induce, either the referral of an individual for, or the purchase, order or recommendation of, any good or service for which payment may be made under federal healthcare programs such as the Medicare and Medicaid programs. This statute has been interpreted to apply to arrangements between pharmaceutical manufacturers, on the one hand, and prescribers, purchasers and formulary managers on the other. The PPACA amends the intent requirement of the federal Anti-Kickback Statute. A person or entity no longer needs to have actual knowledge of this statute or specific intent to violate it;

Table of Contents

- the federal False Claims Act or FCA, which prohibits, among other things, individuals or entities from knowingly presenting, or causing to be presented, claims for payment from Medicare, Medicaid or other third-party payers that are false or fraudulent. Federal Anti-Kickback Statute violations and certain marketing practices, including off-label promotion, also may implicate the FCA;

- federal criminal laws that prohibit executing a scheme to defraud any healthcare benefit program or making false statements relating to healthcare matters;

- the federal Physician Payment Sunshine Act, which requires certain manufacturers of drugs, devices, biologics and medical supplies to report annually to the Centers for Medicare & Medicaid Services, or CMS, information related to payments and other transfers of value to physicians, other healthcare professionals and teaching hospitals, and ownership and investment interests held by physicians and other healthcare professionals and their immediate family members;

- Health Insurance Portability and Accountability Act of 1996, or HIPAA, imposes criminal and civil liability for executing a scheme to defraud any healthcare benefit program or making false statements relating to healthcare matters;

- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, which governs the conduct of certain electronic healthcare transactions and protects the security and privacy of protected health information; and

- state and foreign law equivalents of each of the above federal laws, such as anti-kickback and false claims laws which may apply to: items or services reimbursed by any third-party payer, including commercial insurers; state laws that require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government or otherwise restrict payments that may be made to healthcare professionals and other potential referral sources; state laws that require drug manufacturers to report information related to payments and other transfers of value to physicians and other healthcare professionals or marketing expenditures; and state laws governing the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts.

Violation of any of the laws described above or any other governmental laws and regulations may result in penalties, including civil and criminal penalties, damages, fines, the curtailment or restructuring of operations, the exclusion from participation in federal and state healthcare programs and imprisonment. Furthermore, efforts to ensure that business activities and business arrangements comply with applicable healthcare laws and regulations can be costly for manufacturers of branded prescription products.

Coverage and reimbursement

Significant uncertainty exists as to the coverage and reimbursement status of any products for which we may obtain regulatory approval. In the United States and markets in other countries, sales of any product candidates for which regulatory approval for commercial sale is obtained will depend in part on the availability of coverage and reimbursement from third-party payers. Third-party payers include government authorities, managed care providers, private health insurers and other organizations. The process for determining whether a payer will provide coverage for a drug product may be separate from the process for setting the reimbursement rate that the payer will pay for the drug product. Third-party payers may limit coverage to specific drug products on an approved list, or formulary, which might not include all FDA-approved drugs for a particular indication. Moreover, a payer's decision to provide coverage for a drug product does not imply that an adequate reimbursement rate will be approved.

Third-party payers are increasingly challenging the price and examining the medical necessity and cost-effectiveness of medical products and services, in addition to their safety and efficacy. New metrics frequently are used as the basis

for reimbursement rates, such as Average Selling Price, or ASP, Average Manufacturing Price, or AMP and Actual Acquisition Cost. To obtain coverage and reimbursement for any product that might be approved for sale, it may be necessary to conduct expensive pharmacoeconomic studies to demonstrate the medical necessity and cost-effectiveness of the products, in addition to the costs required to obtain regulatory approvals. If third-party payers do not consider a product to be cost-effective compared to other available therapies, they may not cover the product after approval as a benefit under their plans or, if they do, the level of payment may not be sufficient to allow a company to sell its products at a profit. Health Technology Assessment, or HTA, which is intended to take account of medical, social, economic and ethical issues when determining the suitability of a

Table of Contents

medicinal product for reimbursement is increasingly become an element of the pricing and reimbursement decisions of the competent authorities in European Union Member States.

The United States government, state legislatures and foreign governments have shown significant interest in implementing cost containment programs to limit the growth of government-paid health care costs, including price controls, restrictions on reimbursement and requirements for substitution of generic products for branded prescription drugs. By way of example, the PPACA contains provisions that may reduce the profitability of drug products, including, for example, increasing the minimum rebates owed by manufacturers under the Medicaid Drug Rebate Program, extending the rebate program to individuals enrolled in Medicaid managed care plans, addressing a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted or injected and establishing annual fees based on pharmaceutical companies' share of sales to federal health care programs. Adoption of government controls and measures and tightening of restrictive policies in jurisdictions with existing controls and measures, could limit payments for pharmaceuticals.

With the new Administration and Congress, there likely will be additional legislative changes, including repeal and replacement of certain provisions of the PPACA. To that end, on January 20, 2017, President Trump issued an Executive Order Minimizing the Economic Burden of the PPACA Repeal. The Executive Order declares that, pending repeal of the PPACA, it is imperative for the executive branch to ensure that the law is being efficiently implemented, take all actions consistent with law to minimize the unwarranted economic and regulatory burdens of the PPACA and prepare to provide the states more flexibility and control to create a more free and open healthcare market. The Order directs the Secretary of Health and Human Services and the heads of all other executive departments and agencies with authorities and responsibilities under the PPACA to exercise their authority and discretion to waive, defer, grant exemptions from or delay the implementation of any provision or requirement of the PPACA that would impose a fiscal burden on any state or a cost, fee, tax, penalty or regulatory burden on individuals, families, healthcare professionals, health insurers, patients, recipients of healthcare services, purchasers of health insurance or makers of medical devices, products or medications.

With respect to repeal of the Affordable Care Act and its replacement with new legislation, it is unclear when such legislation will be enacted, what it will provide and what impact it will have on the availability of healthcare and containing or lowering the costs of healthcare.

Additional regulation

In addition to the foregoing, state and federal laws regarding environmental protection and hazardous substances, including the Occupational Safety and Health Act, the Resource Conservation and Recovery Act and the Toxic Substances Control Act, affect our business. These and other laws govern the use, handling and disposal of various biologic, chemical and radioactive substances used in, and wastes generated by, operations. If our operations result in contamination of the environment or expose individuals to hazardous substances, we could be liable for damages and governmental fines. Equivalent laws have been adopted in third countries that impose similar obligations.

U.S. Foreign Corrupt Practices Act

The U.S. Foreign Corrupt Practices Act, or FCPA, prohibits U.S. corporations and individuals from engaging in certain activities to obtain or retain business abroad or to influence a person working in an official capacity. It is illegal to pay, offer to pay or authorize the payment of anything of value to any foreign government official, government staff member, political party or political candidate in an attempt to obtain or retain business or to otherwise influence a person working in an official capacity. The scope of the FCPA includes interactions with certain healthcare professionals in many countries. Equivalent laws have been adopted in other foreign countries that impose similar obligations.

Employees

As of February 15, 2019, we had 368 full-time employees, including a total of 70 employees with M.D. or Ph.D. degrees. Of our workforce, 120 employees are engaged in research and development, 105 employees are engaged in technical operations and manufacturing, 46 employees are engaged in commercial and 97 employees are engaged in

corporate functions, including finance, IT, legal, human resources and general operations and management. None of our employees is represented by a labor union. We consider our relationship with our employees to be good.

Facilities

We occupy approximately 28,000 square feet of office, laboratory and manufacturing space in Philadelphia, Pennsylvania, under a lease that expires in 2025, with our option for early termination in 2021. In February 2016, we entered into a lease for

Table of Contents

approximately 6,500 square feet of additional office space in Philadelphia for corporate and commercial purposes that expires in 2021.

In November 2016, we entered into a lease agreement for approximately 50,000 square feet of office space in Philadelphia, Pennsylvania, that commenced on April 1, 2017. In February 2017, we amended the lease to include approximately 25,000 additional square feet of office space that commenced on January 1, 2018. In November 2017, we amended this lease to accelerate the termination date of approximately 50,000 square feet of office space, with such termination to occur, at the latest, in December 2022.

In November 2017, we entered into a lease in Philadelphia, Pennsylvania for approximately 108,000 square feet of office and laboratory space through June 2033. In October 2018, we amended the lease to include approximately 55,000 additional square feet of office space.

In May 2018, we entered into a lease agreement for approximately 14,000 square feet of office space in Philadelphia, Pennsylvania, that commenced on August 1, 2018 and expires in April 2020.

Corporate information

We were incorporated in the State of Delaware on March 13, 2013. Our principal executive offices are located at 3737 Market Street Suite 1300 Philadelphia, Pennsylvania, and our telephone number is (888) 772-7560.

Our corporate website address is www.sparktx.com. Our website is an inactive textual reference and nothing on our website is incorporated by reference in this Annual Report on Form 10-K. Our Annual Report on Form 10-K, Quarterly Reports on Form 10-Q, Current Reports on Form 8-K and amendments to reports filed pursuant to Sections 13(a) and 15(d) of the Securities Exchange Act of 1934, as amended, or the Exchange Act, are available free of charge on our website as soon as reasonably practicable after we electronically file such material with, or furnish it to, the Securities and Exchange Commission. The Securities and Exchange Commission maintains an internet site that contains our public filings with the Securities and Exchange Commission and other information regarding our company, at www.sec.gov. The contents of these websites are not incorporated into this Annual Report on Form 10-K. Further, our references to the URLs for these websites are intended to be inactive textual reference only.

Legal proceedings

We are not currently a party to any material legal proceedings.

Table of Contents

Item 1A. Risk Factors

The following risk factors and other information included in this Annual Report on Form 10-K should be carefully considered. The risks and uncertainties described below are not the only ones we face. Additional risks and uncertainties not presently known to us or that we presently deem less significant may also impair our business operations. Please see page 5 of this Annual Report on Form 10-K for a discussion of some of the forward-looking statements that are qualified by these risk factors. If any of the following risks occur, our business, financial condition, results of operations and future growth prospects could be materially and adversely affected.

Risks related to the pending transaction with Roche

We may not complete the pending transaction with Roche within the time frame we anticipate, or at all, which could have an adverse effect on our business, financial results and/or operations.

On February 22, 2019, we entered into a definitive merger agreement with Roche Holdings, Inc., or Roche, and 022019 Merger Subsidiary, Inc., a wholly owned subsidiary of Roche, or Merger Sub, or the Merger Agreement. Pursuant to the Merger Agreement, and upon the terms and subject to the conditions thereof, Merger Sub will commence a cash tender offer, or the tender offer, to acquire all of the issued and outstanding shares of our common stock at a price per share of $114.50, net to the seller in cash, without interest, subject to any withholding of taxes required by applicable law. Following the completion of the tender offer, Merger Sub will merge with and into our company, with our company surviving as a wholly owned subsidiary of Roche, and each outstanding share of our common stock (other than shares of common stock held by us as treasury stock, or owned by Roche or Merger Sub or held by stockholders who are entitled to demand, and who properly demand, appraisal rights under Delaware law) will be converted into the right to receive $114.50 per share in cash, without interest, subject to any withholding of taxes required by applicable law.

The completion of the transaction will be conditioned on (1) at least a majority of the shares of our outstanding common stock having been validly tendered into and not withdrawn from the tender offer, (2) receipt of certain regulatory approvals, including expiration of the waiting period under the Hart-Scott-Rodino Antitrust Improvements Act of 1976, (3) the accuracy of certain representations and warranties that we made and compliance by us with certain covenants contained in the Merger Agreement, subject to qualifications, (4) there not having been a “Company Material Adverse Effect” (as defined in the Merger Agreement) with respect to us since the date of the Merger Agreement, and (5) other customary conditions. In addition, the Merger Agreement may be terminated under certain specified circumstances, including, but not limited to, a change in the recommendation of our Board of Directors or a termination of the Merger Agreement by us to enter into an agreement for a “Superior Proposal,” as defined in the Merger Agreement. As a result, we cannot assure you that the transaction with Roche will be completed, or that, if completed, it will be exactly on the terms set forth in the Merger Agreement or within the expected time frame.

If the transaction is not completed within the expected time frame or at all, we may be subject to a number of material risks. The price of our common stock may decline to the extent that current market prices reflect a market assumption that the transaction will be completed. We could be required to pay Roche a termination fee of $144 million if the Merger Agreement is terminated under specific circumstances described in the Merger Agreement. The failure to complete the transaction also may result in negative publicity and negatively affect our relationship with our stockholders, employees, collaborators, customers, regulators and other business partners. We may also be required to devote significant time and resources to litigation related to any failure to complete the merger or related to any enforcement proceeding commenced against us to perform our obligations under the Merger Agreement.

The announcement and pendency of the transaction with Roche could adversely affect our business, financial results and/or operations.

Our efforts to complete the transaction could cause substantial disruptions in, and create uncertainty surrounding, our business, which may materially adversely affect our results of operation and our business. Uncertainty as to whether the transaction will be completed may affect our ability to recruit prospective employees or to retain and motivate existing employees. Employee retention may be particularly challenging while the transaction is pending because employees may experience uncertainty about their roles following the transaction. A substantial amount of our management's and employees' attention is being directed toward the completion of the transaction and thus is being diverted from our day-to-day operations. Uncertainty as to our future could adversely affect our business and our relationship with collaborators, vendors, customers, regulators and other business partners. For example, vendors, collaborators and other counterparties may defer decisions concerning working with us, or seek to change existing business relationships with us. Changes to or termination of existing business relationships could adversely affect our results of operations and financial condition, as well as the market price of our

Table of Contents

common stock. The adverse effects of the pendency of the transaction could be exacerbated by any delays in completion of the transaction or termination of the Merger Agreement.

While the Merger Agreement is in effect, we are subject to restrictions on our business activities.

While the Merger Agreement is in effect, we are subject to restrictions on our business activities, generally requiring us to conduct our business in the ordinary course, consistent with past practice, and subjecting us to a variety of specified limitations absent Roche's prior consent. These limitations include, among other things, restrictions on our ability to acquire other businesses and assets, dispose of our assets, make investments, enter into certain contracts, repurchase or issue securities, pay dividends, make capital expenditures, take certain actions relating to intellectual property, amend our organizational documents and incur indebtedness. These restrictions could prevent us from pursuing strategic business opportunities, taking actions with respect to our business that we may consider advantageous and responding effectively and/or timely to competitive pressures and industry developments, and may as a result materially and adversely affect our business, results of operations and financial condition.

In certain instances, the Merger Agreement requires us to pay a termination fee to Roche, which could require us to use available cash that would have otherwise been available for general corporate purposes.

Under the terms of the Merger Agreement, we may be required to pay Roche a termination fee of $144 million if the Merger Agreement is terminated under specific circumstances described in the Merger Agreement. If the Merger Agreement is terminated under such circumstances, the termination fee we may be required to pay under the Merger Agreement may require us to use available cash that would have otherwise been available for general corporate purposes and other uses. For these and other reasons, termination of the Merger Agreement could materially and adversely affect our business operations and financial condition, which in turn would materially and adversely affect the price of our common stock.

We have incurred, and will continue to incur, direct and indirect costs as a result of the pending transaction with Roche.

We have incurred, and will continue to incur, significant costs and expenses, including fees for professional services and other transaction costs, in connection with the pending transaction. We must pay substantially all of these costs and expenses whether or not the transaction is completed. There are a number of factors beyond our control that could affect the total amount or the timing of these costs and expenses.

Risks related to our financial position

We have incurred net losses since inception. We expect to incur losses for the foreseeable future and may never achieve or maintain profitablity.

We have incurred net losses since inception. Our net losses were $253.5 million and $78.8 million for the years ended December 31, 2017 and 2018, respectively. Our net loss for the year ended December 31, 2018 included a $110.0 million gain from the sale of our priority review voucher during the quarter ended June 30, 2018. As of December 31, 2018, we had an accumulated deficit of $589.7 million. We have financed our operations primarily through private placements of our preferred stock, our IPO, which closed on February 4, 2015, and follow-on offerings which closed on December 28, 2015, June 20, 2016 and August 9, 2017. We received net proceeds from the IPO and follow-on offerings of $775.8 million, after deducting underwriting discounts and commissions and other offering expenses payable by us. We have devoted substantially all our efforts to research and development, including clinical and preclinical development of our product candidates, as well as to building our team and engaging in activities to prepare for commercial launch of LUXTURNA. We expect to continue to incur significant expenses and increasing operating losses for the foreseeable future. The net losses we incur may fluctuate significantly from quarter to quarter. We anticipate that our expenses will increase substantially if, and as, we:

- continue to commercially launch LUXTURNA in the United States;

- seek marketing approvals for any of our product candidates that successfully complete clinical trials;
- continue to grow a marketing and distribution infrastructure to commercialize LUXTURNA in the United States, and any product candidates for which we may submit for and obtain marketing approval anywhere in the world;
- continue our clinical development of our product candidates, including our Phase 1/2 clinical trials for *SPK-7001* and *SPK-8011*;
- conduct IND-enabling studies for our preclinical programs;
- initiate additional preclinical studies and clinical trials for our product candidates;

Table of Contents

- seek to identify additional product candidates;
- build out additional laboratory and current good manufacturing practices, or cGMP, manufacturing capacity;
- further develop our gene therapy platform;
- further expand our medical affairs activities;
- maintain, expand and protect our intellectual property portfolio; and
- acquire or in-license product candidates and technologies.

LUXTURNA is our only product that has been approved for sale and, to date, it only has been approved for the treatment of patients with confirmed biallelic *RPE65* mutation-associated retinal dystrophy who have viable retinal cells as determined by their treating physicians. Our ability to generate revenue will depend on the success of commercial sales of LUXTURNA. However, the successful commercialization of LUXTURNA in the United States is subject to many risks. LUXTURNA is our first commercial launch, and there is no guarantee that we will be able to do so successfully. There are numerous examples of unsuccessful launches where products fail to meet expectations of market potential, including those by pharmaceutical companies with more experience and resources than us. We do not anticipate our revenue from sales of LUXTURNA alone will be sufficient for us to become profitable.

To become and remain profitable, we must develop and commercialize additional product candidates with significant market potential. This will require us to be successful in a range of challenging activities, including completing preclinical testing and clinical trials of our product candidates, obtaining marketing approval for these product candidates, manufacturing, marketing and selling those products for which we may obtain marketing approval and satisfying any post-marketing requirements. We may never succeed in any or all of these activities and, even if we do, we may never generate revenues that are significant enough to achieve profitability. If we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis. Our failure to become and remain profitable would decrease the value of our company and could impair our ability to raise capital, maintain our research and development efforts, expand our business or continue our operations. A decline in the value of our company also could cause our stockholders to lose all or part of their investment.

We have generated limited revenue from product sales and may never be profitable.

Our ability to generate revenue from product sales and achieve profitability depends on our ability, alone or with collaborative partners, to successfully develop and commercialize products.

While we began generating revenue from the sale of LUXTURNA in the first quarter of 2018, we do not expect to achieve profitability unless and until we complete the development of, and obtain the regulatory approvals necessary to commercialize, additional product candidates. Our ability to generate revenues from product sales and achieve profitability depends heavily on our, or our collaborators', success in:

- executing the commercial launch of LUXTURNA;
- maintaining regulatory and marketing approval for LUXTURNA in the United States and the EU;
- seeking and obtaining regulatory and marketing approvals for product candidates for which we complete clinical trials;
- completing research and preclinical and clinical development of our product candidates and identifying new gene therapy product candidates;
- launching and commercializing product candidates for which we obtain regulatory and marketing approval by expanding our existing sales force, marketing and distribution infrastructure or, alternatively, collaborating with a commercialization partner;
- qualifying for, and maintaining, adequate coverage and reimbursement by government and third-party payers on a timely basis for LUXTURNA and any product candidates for which we obtain marketing approval;
- maintaining and enhancing a sustainable, scalable, reproducible and transferable manufacturing process;
- establishing and maintaining supply and manufacturing relationships with third parties that can provide adequate, in both amount and quality, products and services to support clinical development of our product candidates and the market demand for LUXTURNA and any product candidates for which we obtain marketing approval;
- identifying patients eligible for treatment with LUXTURNA for *RPE65*-mediated IRD;
- addressing any competing technological and market developments;
-

implementing additional internal systems and infrastructure, as needed;

Table of Contents

- negotiating favorable terms in any collaboration, licensing or other arrangements into which we may enter and performing our obligations in such collaborations;
- maintaining, protecting and expanding our portfolio of intellectual property rights, including patents, trade secrets and know-how;
- avoiding and defending against third-party interference or infringement claims; and
- attracting, hiring and retaining qualified personnel.

We anticipate incurring significant costs associated with commercializing LUXTURNA in the United States and any other products for which we receive marketing approval. Even with the generation of revenues from sales of LUXTURNA and any other approved products, we may not become profitable and may need to obtain additional funding to continue operations.

Our limited operating history may make it difficult for stockholders to evaluate the success of our business to date and to assess our future viability.

We were founded in March 2013. Our operations to date have been limited to organizing and staffing our company, business planning, raising capital, acquiring technology, identifying potential product candidates and undertaking preclinical studies and clinical trials of our most advanced product candidates, undertaking the commercial launch of LUXTURNA and establishing collaborations. Although we have commenced the initial phases of the commercialization of LUXTURNA, we have no history of commercializing pharmaceutical products, are still in the process of launching LUXTURNA and, to date, have not generated substantial revenue from the sale of LUXTURNA. Consequently, any predictions stockholders make about our future success or viability may not be as accurate as they could be if we had a longer operating history. We are in the early stages of the process of transitioning from a company with a research focus to a company that is also capable of supporting commercial activities. We may not be successful in such a transition.

We may need to raise additional funding, which may not be available on acceptable terms, or at all. Failure to obtain this necessary capital when needed may force us to delay, limit or terminate certain of our product development and commercialization efforts or other operations.

We expect our expenses to increase as we continue the research and development of, and seek marketing approval for, our product candidates. In addition, we expect to incur significant expenses related to product sales, medical affairs, diagnostics, marketing, manufacturing and distribution to support LUXTURNA and any other products for which we obtain marketing approval. Accordingly, we may need to obtain substantial additional funding for our continuing operations. If we are unable to raise capital on attractive terms, or at all, we could be forced to delay, reduce or eliminate certain of our research and development programs and/or commercialization efforts.

Our operations have consumed significant amounts of capital since inception. As of December 31, 2018, our cash and cash equivalents and marketable securities were $548.3 million. Our operating expenses were $258.4 million for the year ended December 31, 2018. We expect to incur significant operating expenses for the foreseeable future. We estimate that our cash and cash equivalents and marketable securities as of December 31, 2018, will enable us to fund our operating expenses and capital expenditure requirements into 2021. We have based this estimate on assumptions that may prove to be wrong, and we could use our available capital resources sooner than we currently anticipate.

Our future capital requirements will depend on many factors, including:

- our execution of our commercial launch of LUXTURNA in the United States;
- the cost and our ability to maintain the commercial infrastructure and manufacturing capabilities required, including product sales, medical affairs, diagnostics, marketing, manufacturing and distribution, to support LUXTURNA in the United States, and any other products for which we receive marketing approval;
- qualifying for, and maintaining adequate coverage and reimbursement by, government and third-party payers on a timely basis for LUXTURNA and any other products for which we obtain marketing approval;
- the costs of preparing and submitting marketing approvals for any of our product candidates that successfully complete clinical trials;
- the costs and timing of manufacturing sufficient supplies of LUXTURNA to meet customer demand;
- the scope, progress, results and costs of drug discovery, recruitment, laboratory testing, preclinical development and clinical trials for our product candidates;

- the costs associated with the build out of additional laboratory and cGMP manufacturing capacity;
- the costs, timing and outcome of regulatory review of our product candidates;

Table of Contents

- revenue received from commercial sales of LUXTURNA and any other products for which we may obtain marketing approval, including amounts reimbursed by government and third-party payers;
- the costs of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending intellectual property-related claims;
- our current collaboration agreements remaining in effect and our achievement of milestones and/or royalty payments under those agreements;
- our ability to establish and maintain additional collaborations on favorable terms, if at all; and
- the extent to which we acquire or in-license product candidates and technologies.

Identifying potential product candidates and conducting preclinical testing and clinical trials is a time-consuming, expensive and uncertain process that takes years to complete. We may never generate the necessary data or results required to obtain marketing approval and achieve product sales for any products other than LUXTURNA. In addition, LUXTURNA or any other products for which we obtain marketing approval may not achieve commercial success. Any product revenues from product candidates, and any commercial milestones or royalty payments under our collaboration agreements will be derived from, or based on, sales of products that may not be commercially available for many years, if at all. Accordingly, we will need to continue to rely on additional financing to achieve our business objectives. To the extent that additional capital is raised through the sale of equity or equity-linked securities, the issuance of those securities could result in substantial dilution for our current stockholders and the terms may include liquidation or other preferences that adversely affect the rights of our current stockholders. Furthermore, the issuance of additional securities, whether equity or debt, by us, or the possibility of such issuance, may cause the market price of our common stock to decline and existing stockholders may not agree with our financing plans or the terms of such financings. Adequate additional financing may not be available to us on acceptable terms, or at all.

Risks related to LUXTURNA

The commercial success of LUXTURNA depends on the extent to which patients, physicians and payers accept and adopt LUXTURNA as a treatment for inherited retinal disease, or IRD, caused by biallelic mutations in the* RPE65 *gene.

The commercial success of LUXTURNA depends on the extent to which patients, physicians and payers accept and adopt LUXTURNA as a treatment for inherited retinal disease, or IRD, caused by biallelic mutations in the *RPE65* gene, and we do not know whether our or others' estimates in this regard will be accurate. While we conduct activities to raise awareness around genetic testing and inherited retinal diseases, there is significant uncertainty in the degree of market acceptance of LUXTURNA. In addition, physicians may not prescribe LUXTURNA, and patients may be unwilling to use LUXTURNA, if coverage is not provided or reimbursement is inadequate. Additionally, the use of LUXTURNA in a non-trial setting may result in unexpected, more serious or a greater incidence of adverse reactions that may negatively affect the commercial prospects of LUXTURNA. Furthermore, a significant negative development in any other gene therapy program or our failure to satisfy any post-marketing regulatory commitments and requirements to which we are or may become subject may adversely impact the commercial results and potential of LUXTURNA. We are conducting a post-marketing observational study of patients treated with LUXTURNA to further evaluate the long-term safety of LUXTURNA. If the results of this long-term study negatively change the benefit/risk profile of LUXTURNA, the commercial results of LUXTURNA and potentially any other product for which we receive marketing approval may be substantially diminished.

As part of our plan to market LUXTURNA in the United States through a limited number of centers that specialize in treating IRDs, we have trained vitreoretinal surgeons to perform the surgical procedure necessary to administer LUXTURNA via sub-retinal injection. This procedure requires significant skill and training. In addition, if we are unable to recruit or train, and thereafter retain, sufficient retinal surgeons to perform the procedure properly, the availability of LUXTURNA could be substantially diminished, which would adversely affect our business, financial condition, results of operations and prospects. Our efforts to educate the medical community and third-party payers on the benefits of LUXTURNA and our product candidates may require significant resources and may never be successful. Such efforts may require more resources than are typically required due to the complexity and uniqueness of LUXTURNA and our other potential products.

We received EMA approval for our marketing authorization application, or MAA, for LUXTURNA in November 2018. The Committee for Medicinal Products for Human Use, or CHMP, adopted a positive opinion on September 21, 2018, recommending approval of LUXTURNA. Even if a product candidate is approved, the European Commission may limit the indications for which the product may be marketed, require extensive warnings on the product labeling or require expensive and time-consuming additional clinical trials or reporting as conditions of approval.

We have entered into a licensing and commercialization agreement with Novartis for the development and commercialization of voretigene neparvovec outside of the United States. The commercial success of voretigene neparvovec outside of the United States depends on Novartis' success at commercializing voretigene neparvovec outside of the United

Table of Contents

States. We have limited control over the amount and timing of resources that Novartis will dedicate to the commercialization of voretigene neparvovec.

If the* RPE65*-mediated IRD patient population is smaller than we estimate, our product revenues may be adversely affected and our business may suffer.

There are several factors that could contribute to making the actual number of patients who receive voretigene neparvovec less than the potentially addressable market. These include the lack of widespread availability of, and limited reimbursement for, new therapies in many underdeveloped markets. Further, the severity of the progression of a disease up to the time of treatment, especially in certain degenerative conditions such as IRDs caused by mutations in the *RPE65* gene, likely will diminish the therapeutic benefit conferred by a gene therapy due to irreversible cell death. In addition, our patient identification efforts may not be successful due to operational challenges or erroneous prevalence and incidence assumptions. Lastly, certain patients' immune systems might prohibit the successful delivery of certain gene therapy products to the target tissue, thereby limiting the treatment outcomes.

If we are unable to obtain adequate coverage of LUXTURNA from third-party payers, the adoption of LUXTURNA by physicians and patients may be limited, which could affect our ability to successfully commercialize LUXTURNA.

While we have reached agreement with certain third-party payers regarding our price for LUXTURNA, we still may receive substantial resistance to our pricing from other third-party payers and the public generally. To assist third-party payers and patients in obtaining and covering LUXTURNA, we have proposed novel payment and distribution programs to assist with the cost of LUXTURNA, including direct sales to payers and outcomes-based rebate arrangements. Even with these programs, there may be substantial resistance to the cost of LUXTURNA by third-party payers and the public generally. Additionally, to the extent reimbursement for LUXTURNA is subject to outcomes-based rebate arrangements, we may be liable for rebate payments in the future. Durability is a factor we use for our outcomes-based rebate arrangements and a negative change in our durability data could negatively impact our ability to successfully commercialize LUXTURNA. These novel payment programs may not be sufficient for third-party payers to grant coverage, and if we are unable to obtain adequate coverage of LUXTURNA, the adoption of LUXTURNA by physicians and patients may be limited. This in turn could affect our ability to successfully commercialize LUXTURNA and adversely impact our business, financial condition, results of operations and prospects.

Risks related to the development of our product candidates

Our gene therapy product candidates are based on a novel technology, which makes it difficult to predict the time and cost of development and of subsequently obtaining regulatory approval.

We have concentrated our research and development efforts on our gene therapy platform, and our future success depends on our successful development of viable gene therapy products. There can be no assurance that we will not experience problems or delays in developing new products and that such problems or delays will not cause unanticipated costs, or that any such development problems can be solved. Currently, LUXTURNA is the only gene therapy product that has been approved for a genetic disease in the United States and only two such products have been approved in the EU. Although we intend to leverage our experience with LUXTURNA in our preclinical and clinical development of product candidates, we may be unable to reduce development timelines and costs for our other gene therapy development programs. We also may experience unanticipated problems or delays in expanding our manufacturing capacity, which may prevent us from completing our clinical trials, meeting the obligations of our collaborations or successfully commercializing LUXTURNA and any other products for which we obtain marketing approval on a timely or profitable basis, if at all. We, a collaborator or another group may uncover a previously unknown risk associated with AAV, and this may prolong the period of observation required for obtaining regulatory approval or may necessitate additional clinical testing.

In addition, the clinical trial requirements of FDA, the European Commission, EMA, the competent authorities of the EU Member States and other regulatory authorities and the criteria these regulators use to determine the safety and efficacy of a product candidate vary substantially according to the type, complexity, novelty and intended use and market of such product candidates. The regulatory approval process for novel product candidates such as ours can be more expensive and take longer than for other, better known or more extensively studied product candidates. Only two

gene therapy products for genetic diseases, uniQure N.V.’s Glybera and GlaxoSmithKline plc's Strimvelis, have received marketing authorization from the European Commission. The marketing authorization for Glybera subsequently expired following the decision of the marketing authorization holder not to apply for a related renewal. LUXTURNA is the only gene therapy product for a genetic disease to have received marketing approval from FDA. We do not yet know if or when it may be authorized by the European Commission. Even if we are successful in developing additional product candidates, it is difficult to determine how long it will take or how much it will cost to obtain regulatory approvals for these product candidates in either the United States or the EU, or how long it will take to commercialize any other products for which we receive marketing approval. In addition, the marketing authorization granted by the European Commission may not be indicative of what FDA may require for approval and vice versa.

Table of Contents

Regulatory requirements governing gene and cell therapy products have changed frequently and may continue to change in the future. FDA has established the Office of Tissue and Advanced Therapies within the Center for Biologics Evaluation and Research, or CBER, to consolidate the review of gene therapy and related products, and has established the Cellular, Tissue and Gene Therapies Advisory Committee to advise CBER in its review. Gene therapy clinical trials conducted at institutions that receive funding for recombinant DNA research from the National Institute of Health, or NIH, also potentially are subject to review by the Regulatory Affairs Certification, or RAC; however, NIH announced in 2014 that the RAC will only publicly review clinical trials if the trials cannot be evaluated by standard oversight bodies and pose unusual risks. Although FDA decides whether individual gene therapy protocols may proceed, the RAC public review process, if undertaken, can delay the initiation of a clinical trial, even if FDA has reviewed the trial design and approved its initiation. Conversely, FDA can put an IND on a clinical hold even if the RAC has provided a favorable review or an exemption from in-depth, public review. If we were to engage an NIH-funded institution, such as CHOP, to conduct a clinical trial, that institution's institutional biosafety committee as well as its institutional review board, or IRB, would need to review the proposed clinical trial to assess the safety of the trial. In addition, adverse developments in clinical trials of gene therapy products conducted by others may cause FDA or other oversight bodies to change the requirements for approval of any of our product candidates. Similarly, the European Commission may issue new guidelines concerning the development and marketing authorization for gene therapy medicinal products and require that we comply with these new guidelines.

These regulatory review committees and advisory groups and the new guidelines they promulgate may lengthen the regulatory review process, require us to perform additional studies, increase our development costs, lead to changes in regulatory positions and interpretations, delay or prevent approval and commercialization of these product candidates or lead to significant post-approval limitations or restrictions. As we advance our product candidates, we will be required to consult with these regulatory and advisory groups and comply with applicable guidelines. If we fail to do so, we may be required to delay or discontinue development of certain of our product candidates. These additional processes may result in a review and approval process that is longer than we otherwise would have expected. Delay or failure to obtain, or unexpected costs in obtaining, the regulatory approval necessary to bring a potential product to market could decrease our ability to generate sufficient product revenue, and our business, financial condition, results of operations and prospects would be materially and adversely affected.

Because we are developing product candidates for the treatment of diseases in which there is little clinical experience and, in some cases, using new endpoints or methodologies, there is increased risk that certain regulatory authorities may not consider the endpoints of our clinical trials to provide clinically meaningful results.

Except for LUXTURNA, there are no pharmacologic therapies approved to treat IRDs caused by the biallelic *RPE65* gene mutations in the United States or EU. In addition, there has been limited clinical trial experience for the development of pharmaceuticals to treat IRDs. Certain aspects of IRDs render efficacy endpoints historically used for vision clinical trials less applicable as clinical endpoints. As a result, the design and conduct of clinical trials for these disorders is subject to increased risk. In addition, the treatment of certain IRDs, such as CHM, may require assessment of clinical endpoints that reflect a stabilization, as opposed to an improvement, of functional vision. Assessing these endpoints may require longer periods of observation and may delay the completion of any trials we may undertake.

Success in preclinical studies or early clinical trials may not be indicative of results obtained in later trials.

Results from preclinical studies or previous clinical trials are not necessarily predictive of future clinical trial results, and interim results of a clinical trial are not necessarily indicative of final results. Our product candidates may fail to show the desired safety and efficacy in clinical development despite demonstrating positive results in preclinical studies or having successfully advanced through initial clinical trials or preliminary stages of clinical trials.

We have limited clinical safety and efficacy data for the use of *SPK-7001* and *SPK-8011* in humans. There can be no assurance that the results seen in preclinical studies for any of our product candidates ultimately will result in success in clinical trials or that results seen in Phase 1 or 2 trials will be replicated in Phase 3 trials. In addition, there can be no assurance that we will be able to achieve the same or similar success in our preclinical studies and clinical trials of our other product candidates.

There is a high failure rate for drugs and biologic products proceeding through clinical trials. Many companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in late-stage clinical trials even after

achieving promising results in preclinical testing and earlier-stage clinical trials. Data obtained from preclinical and clinical activities are subject to varying interpretations, which may delay, limit or prevent regulatory approval. In addition, we may experience regulatory delays or rejections as a result of many factors, including changes in regulatory policy or requirements during the period of our product candidate development. Any such delays could materially and adversely affect our business, financial condition, results of operations and prospects.

Table of Contents

We may find it difficult to enroll subjects in our clinical trials, which could delay or prevent us from proceeding with clinical trials of our product candidates.

Identifying and enrolling appropriate subjects to participate in clinical trials of our product candidates is critical to our success. The timing of the beginning and conclusion of clinical trials depends on our ability to recruit subjects to participate and complete clinical development programs. For example, hemophilia trials often take longer to enroll due to the availability of existing treatments. We have experienced slow enrollment in some of our prior hemophilia trials, and we may experience similar delays in any of our current or future clinical trials. Patients with the disease may be hesitant or unwilling to participate in our gene therapy studies for a variety of reasons: negative publicity from adverse events related to the biotechnology or gene therapy fields, competitive clinical trials for similar patient populations, clinical trials in products employing our vectors or our platform or for other reasons. These factors may delay the timeline for recruiting subjects, conducting studies and obtaining regulatory approval of our product candidates. These delays could result in increased costs, delays in advancing our product candidates, delays in testing the effectiveness of our product candidates or termination of the clinical trials altogether.

We may not be able to identify, recruit and enroll a sufficient number of subjects, or those with required or desired characteristics, to complete our clinical trials in a timely manner. Enrollment and trial completion is affected by factors including:

- size of the patient population and process for identifying subjects;
- design of the trial protocol;
- eligibility and exclusion criteria;
- perceived risks and benefits of the product candidate under study;
- perceived risks and benefits of gene therapy-based approaches to treatment of diseases;
- availability of competing therapies and clinical trials;
- severity of the disease under investigation;
- availability of genetic testing for potential subjects;
- proximity and availability of clinical trial sites for prospective subjects;
- ability to obtain and maintain subject consent;
- risk that enrolled subjects will drop out before completion of the trial;
- patient referral practices of physicians; and
- ability to monitor subjects adequately during and after treatment.

Our current product candidates are being developed to treat rare conditions. For any other product candidate that we successfully develop, we plan to seek initial marketing approvals in the United States and, subsequently, the EU. We may not be able to initiate or continue clinical trials if we cannot enroll a sufficient number of eligible subjects to participate in the clinical trials required by FDA or EMA or other regulatory authorities. Our ability to successfully initiate, enroll and complete a clinical trial in any foreign country is subject to numerous risks unique to conducting business in foreign countries, including:

- difficulty in establishing or managing relationships with contract research organizations, or CROs, and clinical investigators;
- different standards for the conduct of clinical trials;
- absence in some countries of established groups with sufficient regulatory expertise for review of gene therapy protocols;
- our inability to locate qualified local consultants, physicians and partners; and
- the potential burden of complying with a variety of foreign laws, medical standards and regulatory requirements, including the regulation of pharmaceutical and biotechnology products and treatment.

If we have difficulty enrolling a sufficient number of subjects to conduct our clinical trials as planned, we may need to delay, limit or terminate ongoing or planned clinical trials, any of which would have an adverse effect on our business, financial condition, results of operations and prospects.

Table of Contents

We may encounter substantial delays in our clinical trials or we may fail to demonstrate safety or efficacy to the satisfaction of applicable regulatory authorities.

Before obtaining marketing approval from regulatory authorities for the sale of our product candidates, we must conduct extensive clinical trials to demonstrate the safety and efficacy of the product candidates. Clinical testing is expensive, time consuming and uncertain as to outcome. We cannot guarantee that any clinical trials will be conducted as planned or completed on schedule, if at all. A failure of one or more clinical trials can occur at any stage of testing. Events that may prevent successful or timely completion of clinical development include:

- delays in reaching agreement or consensus with regulatory authorities on trial design;
- delays in reaching agreement on acceptable terms with prospective CROs and clinical trial sites;
- delays in opening clinical trial sites or obtaining required IRB or independent Ethics Committee approval at each clinical trial site;
- delays in recruiting suitable subjects to participate in our clinical trials;
- imposition of a clinical hold by regulatory authorities as a result of a serious adverse event, after an inspection of our clinical trial operations or trial sites or for any other reason;
- failure by us, any CROs we engage or any other third parties to adhere to clinical trial requirements;
- failure to perform in accordance with FDA Good Clinical Practice or applicable regulatory guidelines in the EU and other countries;
- delays in the testing, validation, manufacturing and delivery of our product candidates to the clinical sites, including delays by third parties with whom we have contracted to perform certain of those functions;
- delays in having subjects complete participation in a trial or return for post-treatment follow-up;
- clinical trial sites or subjects dropping out of a trial;
- selection of clinical endpoints that require prolonged periods of clinical observation or analysis of the resulting data;
- occurrence of serious adverse events associated with the product candidate that are viewed to outweigh its potential benefits;
- occurrence of serious adverse events in trials of the same class of agents conducted by other sponsors; or
- changes in regulatory requirements and guidance that require amending or submitting new clinical protocols.

Any inability to successfully complete preclinical and clinical development could result in additional costs to us or impair our ability to generate revenues from product sales or to achieve regulatory and commercialization milestones or product royalties. In addition, if we make manufacturing or formulation changes to our product candidates, we may need to conduct additional studies to bridge our modified product candidates to earlier versions. Clinical trial delays also could shorten any periods during which we may have the exclusive right to commercialize our product candidates or allow our competitors to bring products to market before we do, which could impair our ability to successfully commercialize our product candidates and may harm our business, financial condition, results of operations and prospects.

Additionally, if the results of our clinical trials are inconclusive or if there are safety concerns or serious adverse events associated with our product or product candidates, we may:

- be delayed in obtaining marketing approval for our product candidates, if at all;
- obtain approval for indications or patient populations that are not as broad as we intended or desired;
- obtain approval with labeling that includes significant product use or distribution restrictions or safety warnings, including contraindications, warnings or precautions;
- be subject to changes in the way the product is administered;
- be required to perform additional clinical trials to support approval or be subject to additional post-marketing testing requirements;
- have regulatory authorities withdraw, or suspend, their approval of the product or impose restrictions on its distribution in the form of a modified Risk Evaluation and Mitigation Strategy, or REMS, or a similar risk mitigation strategy;
- be sued for alleged injuries caused to patients taking our products; or
- experience damage to our reputation.

42

Table of Contents

Our product and product candidates and the process for administering our product and product candidates may cause undesirable side effects or have other properties that could delay or prevent their regulatory approval, limit the commercial potential or result in significant negative consequences following any potential marketing approval.

There have been several significant adverse side effects in gene therapy treatments in the past, including reported cases of leukemia and death seen in other trials using other vectors. While new recombinant vectors have been developed to reduce these side effects, gene therapy is still a relatively new approach to disease treatment and additional adverse side effects could develop. There also is the potential risk of delayed adverse events following exposure to gene therapy products due to persistent biologic activity of the genetic material or other components of products used to carry the genetic material.

Possible adverse side effects that could occur with treatment with gene therapy products include an immunologic reaction early after administration which, while not necessarily adverse to the patient's health, could substantially limit the effectiveness of the treatment. In previous clinical trials involving AAV vectors for gene therapy, some subjects experienced the development of a T-cell response, whereby after the vector is within the target cell, the cellular immune response system triggers the removal of transduced cells by activated T-cells. If our vectors demonstrate a similar effect, which we are unable to mitigate with immuno-suppressive regimens, we may decide or be required to halt or delay further clinical development of our product candidates and our commercial efforts could be materially and adversely affected.

In addition to any potential side effects caused by the product or product candidate, the administration process or related procedures also can cause adverse side effects. If any such adverse events occur, our marketing authorization or clinical trials could be suspended or terminated. For example, FDA placed our second open-label Phase 1 clinical trial for LUXTURNA, which we refer to as our 102 trial, on a clinical hold temporarily when we voluntarily halted enrollment and reported a serious adverse event arising from a steroid injection given following administration of LUXTURNA to manage post-operative inflammation related to the standard vitrectomy procedure subjects undergo prior to administration of LUXTURNA. We subsequently adjusted the protocol regarding the use of local steroids and FDA released the clinical hold, allowing the trial to proceed.

If in the future we are unable to demonstrate that such adverse events were caused by the administration process or related procedures, FDA, the European Commission, EMA or other regulatory authorities could order us to cease further development of, or deny approval of, our product candidates for any or all targeted indications. Even if we can demonstrate that all future serious adverse events are not product-related, such occurrences could affect patient recruitment or the ability of enrolled patients to complete the trial. Moreover, if we elect, or are required, to delay, suspend or terminate any clinical trial of any of our product candidates, the commercial prospects of such product candidates may be harmed and our ability to generate product revenues from any of these product candidates may be delayed or eliminated. Any of these occurrences may harm our ability to develop other product candidates, and may harm our business, financial condition and prospects significantly.

In addition, FDA could impose a REMS, and other non-US regulatory authorities could impose other specific obligations as a condition of approval to ensure that the benefits of our product candidates outweigh their risks, which could delay approval or commercial acceptance of our product candidates. A REMS may include, among other things, a communication plan to health care practitioners or patients, and elements to assure safe use, such as restricted distribution methods, patient registries, and other risk minimization tools. Similar risk management programs could be imposed by equivalent authorities in foreign jurisdictions, including by the European Commission. Furthermore, if we or others later identify undesirable side effects caused by our product candidate, several potentially significant negative consequences could result, including:

- regulatory authorities may suspend or withdraw approvals of such product candidate;
- regulatory authorities may require additional warnings or limitations of use in product labeling;
- we may be required to change the way a product candidate is administered or conduct additional clinical trials;
- we could be sued and held liable for harm caused by our products to patients; and
- our reputation may suffer.

Any of these events could prevent us from achieving or maintaining market acceptance of LUXTURNA and any other products for which we receive marketing approval and could significantly harm our business, financial condition, results of operations and prospects.

We may be unable to obtain additional orphan drug designations or obtain and maintain orphan drug exclusivity for any product. If a competitor obtains orphan drug exclusivity for its product and the regulatory authority subsequently determines that our product candidate is the same drug and treats the same indication(s) as the previously approved product, we may not be able to get our product approved until after the orphan drug exclusivity period has ended.

Regulatory authorities in some jurisdictions, including the United States and the EU, may designate drugs for relatively small patient populations as orphan drugs. Under the Orphan Drug Act of 1983, FDA may designate a product candidate as an

Table of Contents

orphan drug if it is intended to treat a rare disease or condition, which is generally defined as having a patient population of fewer than 200,000 individuals in the United States, or a patient population greater than 200,000 in the United States where there is no reasonable expectation that the cost of developing the drug will be recovered from sales in the United States. In the EU, EMA's Committee for Orphan Medicinal Products grants orphan drug designation to promote the development of products that are intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than 5 in 10,000 persons in the EU. Additionally, orphan designation is granted for products intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition and when, without incentives, it is unlikely that sales of the drug in the EU would be sufficient to justify the necessary investment in developing the drug or biologic product. Similar "orphan drug" designations exist in some, but not all, jurisdictions outside the EU and the United States.

Upon approval, LUXTURNA was granted orphan drug exclusivity by FDA for the treatment of IRD caused by biallelic mutations to the *RPE65* gene. Pursuant to such orphan drug exclusivity in the United States, FDA is precluded, subject to certain exceptions discussed below, from approving another marketing application for a product that constitutes the same drug treating the same indication for a seven-year period, which exclusivity period can be extended by six months under certain circumstances as discussed below. Orphan drug designation does not guarantee orphan drug exclusivity and a designated orphan drug will be denied market approval if it is blocked by the orphan exclusivity of a previously approved orphan product.

LUXTURNA has received an orphan drug designation from the European Commission for the treatment of both LCA and RP due to *RPE65* mutations. *SPK-9001* has received both breakthrough therapy and orphan drug designation by FDA. *SPK-8011* has received breakthrough therapy designation by FDA. *SPK-7001* has been granted orphan drug designation by FDA and the European Commission for the treatment of CHM. *SPK-TPP1* has been granted orphan product designation by FDA for the treatment of CLN2 disease (neuronal ceroid lipofuscinosis (NCL)) caused by TPP1 deficiency.

If we request orphan drug designation for our other current or future product candidates, there can be no assurances that FDA or the European Commission will grant any of our product candidates such designation. Additionally, the designation of any of our product candidates as an orphan product does not guarantee that any regulatory agency will accelerate regulatory review of, or ultimately approve, that product candidate, nor does it limit the ability of any regulatory agency to grant orphan drug designation to product candidates of other companies that treat the same indications as our product candidates prior to our product candidates receiving exclusive marketing approval. Generally, if a product candidate with an orphan drug designation receives the first marketing approval for the indication for which it has such designation, the product is entitled to a period of marketing exclusivity, which precludes FDA or the European Commission from approving another marketing application for a product that constitutes the same drug treating the same disease or condition for that marketing exclusivity period, except in limited circumstances. If another sponsor receives approval before we do (regardless of our orphan drug designation), we would be precluded from receiving marketing approval for our product if it is the same product approved for the same disease or condition for the applicable exclusivity period. The applicable period is seven years in the United States and 10 years in the EU. The exclusivity period in the United States can be extended by six months if the BLA sponsor submits pediatric data that fairly respond to a written request from FDA for such data. The exclusivity period in the EU can be reduced to six years if, at the end of the fifth year, it is established that the orphan designation criteria are no longer met, e.g., where a product no longer meets the criteria for orphan drug designation or if the product is sufficiently profitable so that market exclusivity is no longer justified. Orphan drug exclusivity may be revoked if any regulatory agency determines that the request for designation was materially defective or if the manufacturer is unable to assure sufficient quantity of the product to meet the needs of patients with the rare disease or condition.

Even if we maintain orphan drug exclusivity for LUXTURNA or obtain orphan drug exclusivity for a product candidate, that exclusivity may not effectively protect the product candidate from competition because different drugs can be approved for the same disease or condition. In the United States, even after an orphan drug is approved, FDA may subsequently approve another drug for the same condition if FDA concludes that the latter drug is not the same drug or is clinically superior in that it is shown to be safer, more effective or makes a major contribution to patient

care or the exclusivity holder consents to the approval of another product or if the sponsor cannot supply a sufficient quantity of the product. It is unclear what criteria regulatory authorities will use for gene therapies to determine similarity under orphan drug designation. In the EU, marketing authorization may be granted to a similar medicinal product for the same orphan indication if the second applicant can establish in its application that its medicinal product, although similar to the orphan medicinal product already authorized, is safer, more effective or otherwise clinically superior, if the holder of the marketing authorization for the original orphan medicinal product consents to a second orphan medicinal product application, or if the holder of the marketing authorization for the original orphan medicinal product cannot supply sufficient quantities of orphan medicinal product.

Breakthrough therapy designation by FDA may not lead to a faster development, regulatory review or approval process and it does not increase the likelihood that any of our product candidates will receive marketing approval in the United States.

Table of Contents

We have received breakthrough therapy designation for *SPK-9001* for the treatment of hemophilia B and *SPK-8011* for the treatment of hemophilia A. We may, in the future, apply for breakthrough therapy designation for other product candidates in the United States. A breakthrough therapy product candidate is defined as a product candidate that is intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that such product candidate may demonstrate substantial improvement on one or more clinically significant endpoints over existing therapies. FDA will seek to ensure the sponsor of a breakthrough therapy product candidate receives: (i) intensive guidance on an efficient drug development program; (ii) intensive involvement of senior managers and experienced staff on a proactive, collaborative and cross-disciplinary review; and (iii) a rolling review process whereby FDA may consider reviewing portions of a BLA before the sponsor submits the complete application. Product candidates designated as breakthrough therapies by FDA may be eligible for priority review if supported by clinical data.

Designation as a breakthrough therapy is within the discretion of FDA. Accordingly, even if we believe one of our product candidates meets the criteria for designation as a breakthrough therapy, FDA may disagree. In any event, the receipt of a breakthrough therapy designation, or the redemption of a Rare Pediatric Disease Priority Review Voucher for a product candidate, may not result in a faster development process, review or approval compared to products considered for approval under conventional FDA procedures and, in any event, does not assure ultimate approval by FDA. In addition, even though *SPK-9001* and *SPK-8011* have been designated as breakthrough therapy product candidates, FDA may later decide that either or both no longer meet the conditions for designation and revoke it or decide that the application for the product will not receive priority review.

Even if we complete the necessary clinical trials, we cannot predict when, or if, we will obtain regulatory approval to commercialize a product candidate and the approval may be for a narrower indication than we seek.

We cannot commercialize a product candidate until the appropriate regulatory authorities have reviewed and approved the product candidate. Even if our product candidates meet their safety and efficacy endpoints in clinical trials, the regulatory authorities may not complete their review processes in a timely manner, or we may not be able to obtain regulatory approval. Additional delays may result if an FDA Advisory Committee or other regulatory authority recommends non-approval or restrictions or conditions on approval. In addition, we may experience delays or rejections based upon additional government regulation from future legislation or administrative action, or changes in regulatory authority policy during the period of product development, clinical trials and the review process.

Regulatory authorities also may approve a product candidate for more limited indications than requested or they may impose significant limitations in the form of narrow indications, contraindications or a REMS. These regulatory authorities may require warnings or precautions with respect to conditions of use or they may grant approval subject to the performance of costly post-marketing clinical trials. In addition, regulatory authorities may not approve the labeling claims or allow the promotional claims that are necessary or desirable for the successful commercialization of our product candidates. Any of the foregoing scenarios could materially harm the commercial prospects for our product candidates and materially and adversely affect our business, financial condition, results of operations and prospects.

Further, the regulatory authorities may require concurrent approval, or CE marking, of a companion diagnostic device. For the product candidates we currently are developing, we believe that diagnoses based on symptoms, in conjunction with existing genetic tests developed and administered by laboratories certified under the Clinical Laboratory Improvement Amendments, or CLIA, are sufficient to diagnose patients and, with respect to LUXTURNA, have been permitted by FDA. For future product candidates, however, it may be necessary to use FDA-cleared or FDA-approved diagnostic tests or equivalent tests approved by foreign authorities or CE marked in the EU to diagnose patients or to assure the safe and effective use of product candidates in trial subjects. FDA refers to such tests as *in vitro* companion diagnostic devices. On July 31, 2014, FDA announced the publication of a final guidance document describing the agency's current thinking about the development and regulation of *in vitro* companion diagnostic devices. The final guidance articulates a policy position that, when safe and effective use of a therapeutic product depends on a diagnostic device, FDA generally will require approval or clearance of the diagnostic device when FDA approves the therapeutic product. The final guidance allows for two exceptions to the general rule of concurrent drug/device approval, namely, when the therapeutic product is intended to treat serious and life-threatening conditions for which

no alternative exists, and when a serious safety issue arises for an approved therapeutic agent, and no FDA-cleared or FDA-approved companion diagnostic test is yet available. At this point, it is unclear how FDA will apply this policy to our current or future gene therapy product candidates. Should FDA deem genetic tests used for diagnosing patients for our therapies to be *in vitro* companion diagnostics requiring FDA clearance or approval, we may face significant delays or obstacles in obtaining approval of a BLA for our product candidates. In the EU, Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices will apply from 2022 and repeal the current applicable provisions. Regulation (EU) 2017/746 will impose additional obligations on us that may impact the development and authorization of our product candidates in the EU.

Even if we obtain regulatory approval for a product candidate, our products will remain subject to regulatory oversight.

Table of Contents

LUXTURNA, and any of our product candidates for which we obtain regulatory approval, will be subject to ongoing regulatory requirements for manufacturing, labeling, packaging, storage, advertising, promotion, record-keeping and submission of safety and other post-market information. Any regulatory approvals that we receive for our product candidates also may be subject to a REMS or the specific obligations imposed as a condition for marketing authorization by equivalent authorities in a foreign jurisdiction, particularly by the European Commission, limitations on the approved indicated uses for which the product may be marketed or to the conditions of approval, or contain requirements for potentially costly post-marketing testing, including Phase 4 clinical trials, and surveillance to monitor the quality, safety and efficacy of the product. For example, in the United States, the holder of an approved BLA is obligated to monitor and report adverse events and any failure of a product to meet the specifications in the BLA. FDA guidance advises that patients treated with some types of gene therapy undergo follow-up observations for potential adverse events for as long as 15 years, and each of our clinical trials includes a 15-year long-term follow-up phase. The holder of an approved BLA also must submit new or supplemental applications and obtain FDA approval for certain changes to the approved product, product labeling or manufacturing process. Advertising and promotional materials must comply with the Federal Food Drug and Cosmetic Act and implementing regulations and are subject to FDA oversight and post-marketing reporting obligations, in addition to other potentially applicable federal and state laws.

In the EU, the advertising and promotion of our products are subject to EU laws governing promotion of medicinal products, interactions with physicians, misleading and comparative advertising and unfair commercial practices. In addition, other legislation adopted by individual EU Member States may apply to the advertising and promotion of medicinal products. These laws may limit or restrict the advertising and promotion of our products to the general public and may impose limitations on our promotional activities with health care professionals. These laws require that promotional materials and advertising for medicinal products are consistent with the product's Summary of Product Characteristics, or SmPC, as approved by the competent authorities. The SmPC is the document that provides information to physicians concerning the safe and effective use of the medicinal product. It forms an intrinsic and integral part of the marketing authorization granted for the medicinal product. Promotion of a medicinal product that does not comport with the SmPC is considered to constitute off-label promotion, which is prohibited in the EU. The applicable laws at EU level and in the individual EU Member States also prohibit the direct-to-consumer advertising of prescription-only medicinal products. Violations of the rules governing the promotion of medicinal products in the EU could be penalized by administrative measures, fines and imprisonment.

In addition, product manufacturers and their facilities may be subject to payment of application and program fees and are subject to continual review and periodic inspections by FDA and other regulatory authorities for compliance with current cGMP, requirements and adherence to commitments made in the BLA or foreign marketing application. If we, or a regulatory authority, discover previously unknown problems with a product, such as adverse events of unanticipated severity or frequency, or problems with the facility where the product is manufactured or disagrees with the promotion, marketing or labeling of that product, a regulatory authority may impose restrictions relative to that product, the manufacturing facility or us, including requiring recall or withdrawal of the product from the market or suspension of manufacturing.

If we fail to comply with applicable regulatory requirements for LUXTURNA or for any other product following approval, a regulatory authority may:

- issue a warning letter asserting that we are in violation of the law;
- seek an injunction or impose administrative, civil or criminal penalties or monetary fines;
- suspend or withdraw regulatory approval;
- suspend any ongoing clinical trials;
- refuse to approve a pending BLA or comparable foreign marketing application (or any supplements thereto) submitted by us or our strategic partners;
- restrict the marketing or manufacturing of the product;
- seize or detain the product or otherwise demand or require the withdrawal or recall of the product from the market;
- refuse to permit the import or export of products;
- request and publicize a voluntary recall of the product; or

- refuse to allow us to enter into supply contracts, including government contracts.

Any government investigation of alleged violations of law could require us to expend significant time and resources in response and could generate negative publicity. The occurrence of any event or penalty described above may inhibit our ability to commercialize our product candidates and adversely affect our business, financial condition, results of operations and prospects.

Table of Contents

In addition, FDA's policies, and those of equivalent foreign regulatory agencies, may change and additional government regulations may be enacted that could prevent, limit or delay regulatory approval of our product candidates. We cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative action, either in the United States or abroad. If we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we are not able to maintain regulatory compliance, we may lose any marketing approval that we may have obtained and we may not achieve or sustain profitability, which would materially and adversely affect our business, financial condition, results of operations and prospects.

Both marketing authorization holders and manufacturers of medicinal products are subject to comprehensive regulatory oversight by EMA and the competent authorities of the individual EU Member States both before and after grant of the manufacturing and marketing authorizations. This includes control of compliance with cGMP rules, which govern quality control of the manufacturing process and require documentation policies and procedures. We and our third-party manufacturers would be required to ensure that our processes, methods, and equipment are compliant with cGMP. Failure by us or by any of our third-party partners, including suppliers, manufacturers, and distributors to comply with EU laws and the related national laws of individual EU Member States governing the conduct of clinical trials, manufacturing approval, marketing authorization of medicinal products, both before and after grant of marketing authorization, and marketing of such products following grant of authorization may result in administrative, civil, or criminal penalties. These penalties could include delays in or refusal to authorize the conduct of clinical trials or to grant marketing authorization, product withdrawals and recalls, product seizures, suspension, or variation of the marketing authorization, total or partial suspension of production, distribution, manufacturing, or clinical trials, operating restrictions, injunctions, suspension of licenses, fines, and criminal penalties.

In addition, EU legislation related to pharmacovigilance, or the assessment and monitoring of the safety of medicinal products, provides that EMA and the competent authorities of the EU Member States have the authority to require companies to conduct additional post-approval clinical efficacy and safety studies. The legislation also governs the obligations of marketing authorization holders with respect to additional monitoring, adverse event management and reporting. Under the pharmacovigilance legislation and its related regulations and guidelines, we may be required to conduct a burdensome collection of data regarding the risks and benefits of marketed products and may be required to engage in ongoing assessments of those risks and benefits, including the possible requirement to conduct additional clinical studies, which may be time-consuming and expensive and could impact our profitability. Non-compliance with such obligations can lead to the variation, suspension or withdrawal of marketing authorization or imposition of financial penalties or other enforcement measures.

We face significant competition in an environment of rapid technological change and the possibility that our competitors may achieve regulatory approval before us or develop therapies that are more advanced or effective than ours, which may adversely affect our financial condition and our ability to successfully market or commercialize our product and product candidates.

The biotechnology and pharmaceutical industries, including the gene therapy field, are characterized by rapidly changing technologies, significant competition and a strong emphasis on intellectual property. We face substantial competition from many different sources, including large and specialty pharmaceutical and biotechnology companies, academic research institutions, government agencies and public and private research institutions.

We are aware of companies focused on developing AAV gene therapies in various indications, including 4D Molecular Therapeutics, Abeona Therapeutics Inc., Actus Therapeutics, Inc., Adverum Biotechnologies, Inc., Amicus Therapeutics, Inc., Applied Genetic Technologies Corporation, Asklepios BioPharmaceutical, Inc., Audentes Therapeutics, Inc., Axovant Sciences, Inc., BioMarin Pharmaceutical Inc., GenSight Biologics SA, Homology Medicines, Inc., Horama SAS, Lysogene SAS, MeiraGTx Limited, Nightstar Therapeutics plc., PTC Therapeutics, Inc., REGENXBIO, Inc., Sangamo Therapeutics, Inc., Sarepta Therapeutics, Inc., Solid Biosciences, Inc., Ultragenyx Pharmaceuticals, Inc., uniQure N.V. and Voyager Therapeutics, Inc., as well as several companies addressing other methods for delivering or modifying genes and regulating gene expression. Any advances in gene therapy technology made by a competitor may be used to develop therapies that could compete against LUXTURNA and any of our product candidates.

For LUXTURNA and clinical product candidates we are developing, the main competitors include:

LUXTURNA. While no other approved pharmacologic agents exist for patients with *RPE65*-mediated IRD, Second Sight Medical Products, Inc. has received approval from FDA and other foreign regulatory authorities for a retinal prosthesis medical device, which is being marketed to RP patients with limited or no light perception. Another retinal prosthesis medical device from Retina Implant AG has obtained a CE Certificate of Conformity from its notified body, and is similarly indicated for blinded patients. Novelion Therapeutics, Inc. (formally QLT Inc.) completed a Phase 1b clinical trial of a vitamin A derivative to treat RP and LCA. In the gene therapy space, certain companies and several

Table of Contents

academic institutions have conducted or plan to conduct clinical trials involving *RPE65*-based product candidates, including MeiraGTx and Horama SAS. To date, none of these organizations has completed a trial involving injection of a subject's second eye or has initiated a Phase 3 trial.

- ***SPK-CHM.*** We are aware that Nightstar Therapeutics plc, or Nightstar, is developing an AAV-based gene therapy for the treatment of choroideremia. Nightstar has obtained orphan product designation in the United States and the European Union for this product candidate for the treatment of choroideremia and has announced that it has initiated a Phase 3 trial for choroideremia. We are also aware that 4D Molecular Therapeutics and F. Hoffmann-La Roche AG have pre-clinical programs in process.
- ***SPK-FVIII.*** The standard of care for moderate to severe hemophilia A patients is intravenously administered factor VIII protein or its derivatives that are produced by several companies. There are other companies developing gene therapies to treat hemophilia A, including BioMarin Pharmaceutical Inc., Ultragenyx Pharmaceuticals, Inc., in collaboration with Bayer HealthCare, Shire PLC, uniQure N.V., Sangamo Therapeutics, Inc. in collaboration with Pfizer and Telethon Institute for Gene Therapy in collaboration with Sanofi.

Many of our potential competitors, alone or with their strategic partners, have substantially greater financial, technical and other resources, such as larger research and development, clinical, marketing and manufacturing organizations. Mergers and acquisitions in the biotechnology and pharmaceutical industries may result in even more resources being concentrated among a smaller number of competitors. Our commercial opportunity could be reduced or eliminated if competitors develop and commercialize products that are safer, more effective, have fewer or less severe side effects, are more convenient or are less expensive than any products that we may develop. Competitors also may obtain FDA or other regulatory approval for their products more rapidly or earlier than we may obtain approval for ours, which could result in our competitors establishing a strong market position before we are able to enter the market. Additionally, technologies developed by our competitors may render our product or product candidates uneconomical or obsolete, and we may not be successful in marketing our product or product candidates against competitors.

In addition, as a result of the expiration or successful challenge of our patent rights, we could face more litigation with respect to the validity and/or scope of patents relating to our competitors' products. The availability of our competitors' products could limit the demand, and the price we are able to charge, for any products that we may develop and commercialize.

Even if we obtain and maintain approval for product candidates from FDA, we may never obtain approval for our product candidates outside of the United States, which would limit our market opportunities and adversely affect our business.

Approval of a product candidate in the United States by FDA does not ensure approval of such product candidate by regulatory authorities in other countries or jurisdictions, and approval by one foreign regulatory authority does not ensure approval by regulatory authorities in other foreign countries or by FDA. Sales of our product candidates outside of the United States will be subject to foreign regulatory requirements governing clinical trials and marketing approval. Even if FDA grants marketing approval for a product candidate, comparable regulatory authorities of foreign countries also must approve the manufacturing and marketing of the product candidates in those countries. Approval procedures vary among jurisdictions and can involve requirements and administrative review periods different from, and more onerous than, those in the United States, including additional preclinical studies or clinical trials. In many countries outside the United States, a product candidate must be approved for reimbursement before it can be approved for sale in that country. In some cases, the price that we intend to charge for our products, if approved, is also subject to approval. We intend to submit to the EMA for approval of our product candidates in the EU, but obtaining such approval from the European Commission following the opinion of EMA is a lengthy and expensive process. When an MAA is submitted to the EMA, a related scientific evaluation is conducted by EMA's CHMP and a scientific opinion is prepared concerning the suitability of the product for authorization. This scientific opinion is sent to the European Commission which, before arriving at a final decision on an MAA, must consult the Standing Committee on Medicinal Products for Human Use. The Standing Committee is composed of representatives of the EU Members States and chaired by a non-voting European Commission representative. The European Parliament also has a related "droit de regard". The European Parliament's role is to ensure that the European Commission has not exceeded its powers in deciding to grant or refuse to grant a marketing authorization. In

accordance with the centralized procedure, the maximum timeframe for the evaluation of an MAA is 210 days. This excludes clock stops during which additional information or written or oral explanations are provided by the applicant in response to questions posed by the CHMP. The CHMP adopted a positive opinion on September 21, 2018, recommending approval of LUXTURNA.

Even if a product candidate is approved, FDA or the European Commission may limit the indications for which the product may be marketed, require extensive warnings on the product labeling or require expensive and time-consuming additional clinical trials or reporting as conditions of approval.

Regulatory authorities in countries outside of the United States and the EU also have requirements for approval of product candidates with which we must comply prior to marketing in those countries. Obtaining foreign regulatory approvals and

Table of Contents

compliance with foreign regulatory requirements could result in significant delays, difficulties and costs for us and could delay or prevent the introduction of our product candidates in certain countries.

Further, clinical trials conducted in one country may not be accepted by regulatory authorities in other countries. Also, regulatory approval for any of our product candidates may be withdrawn. If we fail to comply with regulatory requirements, our target market will be reduced and our ability to realize the full market potential of our product candidates will be harmed and our business, financial condition, results of operations and prospects will be adversely affected.

Risks related to the commercialization of LUXTURNA and our product candidates for which we obtain marketing approval

If we are unable to expand our market development capabilities or enter into agreements with third parties to market and sell any of our product candidates for which we obtain marketing approval, we may be unable to generate any product revenue.

To successfully commercialize any products that may result from our development programs, we need to continue to expand our market development capabilities, either on our own or with others. The development of our own market development effort is, and will continue to be, expensive and time-consuming and could delay any product launch. Moreover, we cannot be certain that we will be able to successfully develop this capability.

We have entered into a collaboration with Pfizer for the development and commercialization of *SPK-FIX* product candidates for the treatment of hemophilia B pursuant to which Pfizer would commercialize such product candidates, and we would be eligible to receive specified milestone payments and royalties, for any product developed under the agreement. We have entered into a license and commercialization agreement with Novartis for the development and commercialization of investigational voretigene neparvovec outside the United States, and we are eligible to receive specified milestone payments and royalties pursuant to that agreement. We may enter into collaborations regarding other of our product candidates with other entities to utilize their established marketing and distribution capabilities, but we may be unable to enter into such agreements on favorable terms, if at all. If any current or future collaborators do not commit sufficient resources to commercialize our products, or we are unable to develop the necessary capabilities on our own, we will be unable to generate sufficient product revenue to sustain our business. We compete with many companies that currently have extensive, experienced and well-funded medical affairs, marketing and sales operations to recruit, hire, train and retain marketing and sales personnel. We also face competition in our search for third parties to assist us with the sales and marketing efforts of our product candidates. Without an internal team or the support of a third party to perform marketing and sales functions, we may be unable to compete successfully against these more established companies.

If the market opportunities for our product candidates are smaller than we believe they are, our product revenues may be adversely affected and our business may suffer.

We focus our research and product development on treatments for severe genetic and orphan diseases. Our understanding of both the number of people who have these diseases, as well as the subset of people with these diseases who have the potential to benefit from treatment with our product candidates, are based on estimates. These estimates may prove to be incorrect and new studies may reduce the estimated incidence or prevalence of these diseases. The number of patients in the United States, the EU and elsewhere may turn out to be lower than expected, may not be otherwise amenable to treatment with our products or patients may become increasingly difficult to identify and access, all of which would adversely affect our business, financial condition, results of operations and prospects.

Further, there are several factors that could contribute to making the actual number of patients who receive other potential products less than the potentially addressable market. These include the lack of widespread availability of, and limited reimbursement for, new therapies in many underdeveloped markets. Further, the severity of the progression of a disease up to the time of treatment, especially in certain degenerative conditions, will likely diminish the therapeutic benefit conferred by a gene therapy due to irreversible cell death. Lastly, certain patients' immune systems might prohibit the successful delivery of certain gene therapy products to the target tissue, thereby limiting the treatment outcomes.

Our business could be affected by government price controls or other changes in pricing regulation could restrict the amount that we are able to charge for our product and any of our product candidates that may be approved in the future, which would adversely affect our revenue and results of operations.

We expect that coverage and reimbursement of pharmaceutical drugs may be increasingly restricted both in the United States and internationally. The escalating cost of health care has led to increased pressure on the health care industry to reduce costs. In particular, increased public scrutiny has been placed on wholesale prices of drugs, and such prices continue to be subject to intense political and public debate in the United States and abroad. Government and private third-party payers have proposed health care reforms and cost reductions. A number of federal and state proposals to control the cost of health care, including the cost of drug treatments, have been made in the United States. Specifically, there have been several recent United States Congressional inquiries and proposed federal and state bills designed to, among other things, bring more transparency to

Table of Contents

drug pricing, review the relationship between pricing and manufacturer patient programs and reform government program reimbursement methodologies for drugs. At least seven states have passed legislation related to drug price transparency and many others have pending legislation. In addition, there have been proposals to impose federal rebates on Medicare Part D drugs, which would require federally-mandated rebates on either all drugs dispensed to Medicare Part D beneficiaries or on only those drugs dispensed to certain groups of lower income beneficiaries. In some international markets, the government controls the pricing, which can affect the profitability of drugs. Current government regulations and possible future legislation regarding health care may affect coverage and reimbursement for medical treatment by third-party payers, which may render our product or any product candidates for which we obtain marketing approval not commercially viable or may adversely affect our anticipated future revenues and gross margins.

In 2018, President Trump released the Blueprint to Lower Drug Prices and Reduce Out-of-Pocket Costs, or Blueprint. Certain proposals in the Blueprint seek to encourage innovation and expand outcome-based payments in Medicare and Medicaid and may cause significant operational and reimbursement changes for the pharmaceutical industry. We cannot predict whether the Blueprint may affect our ongoing discussions with CMS to align on our proposal for an installment payment option and flexibility to offer greater outcomes-based rebates.

In late 2018, CMS issued an advance notice of proposed rulemaking, or ANPRM, describing a potential mandatory model to test Medicare reimbursement based on an "International Pricing Index", or IPI. CMS is considering issuing a proposed rule that would describe the model in more detail in spring 2019, with the goal of starting the model in spring 2020. If a model would proceed as described, we cannot predict the requisite infrastructure and reporting requirements, existing and new data sources required to establish an IPI and target price and the impact on price reporting and reporting mechanics.

We cannot predict the extent to which our business may be affected by these or other potential future legislative or regulatory developments. However, future price controls or other changes in pricing regulation or negative publicity related to the pricing of pharmaceutical drugs generally could restrict the amount that we are able to charge for our future products, which would adversely affect our anticipated revenue and results of operations.

The insurance coverage and reimbursement status of newly approved products is uncertain. Failure to obtain or maintain adequate coverage and reimbursement for our products and any future products, if approved, could limit our ability to market those products and decrease our ability to generate product revenue.

The cost of a single administration of gene therapy products can be substantial. We expect that coverage and reimbursement by government and commercial payers will be essential for most patients to be able to afford these treatments. Accordingly, sales of our product, and any product candidates for which we obtain marketing approval, will depend substantially, both domestically and abroad, on the extent to which the prices of such product candidates will be paid by health maintenance, managed care, pharmacy benefit and similar healthcare management organizations, or will be reimbursed by government authorities, private health coverage insurers and other third-party payers. Coverage and reimbursement by a third-party payer may depend upon several factors, including the third-party payer’s determination that use of a product is:

- a covered benefit under its health plan;
- safe, effective and medically necessary;
- appropriate for the specific patient;
- cost-effective; and
- neither experimental nor investigational.

Obtaining coverage and reimbursement for a product from third-party payers is a time-consuming and costly process that could require us to provide to the payer supporting scientific, clinical and cost-effectiveness data. We may not be able to provide data sufficient to gain acceptance with respect to coverage and reimbursement.

There is significant uncertainty related to third-party coverage and reimbursement of newly approved products, including potential one-time gene therapies. In the United States, third-party payers, including government payers such as the Medicare and Medicaid programs, play an important role in determining the extent to which new drugs and biologics will be covered and reimbursed. The Medicare and Medicaid programs increasingly are used as models for how private payers and government payers develop their coverage and reimbursement policies. LUXTURNA has

been approved for coverage and reimbursement by the Centers for Medicare and Medicaid Services, or CMS, the agency responsible for administering the Medicare program. We cannot be assured that Medicare or Medicaid will cover any other approved products or provide reimbursement at adequate levels to realize a sufficient return on our investment. Moreover, reimbursement agencies in the EU may be more conservative than CMS. For example, several cancer drugs have been approved for reimbursement in the United States and have not been approved for reimbursement in certain EU Member States. It is difficult to predict what third-party payers will decide with respect to the coverage and reimbursement for our products for which we obtain marketing approval.

Table of Contents

Outside the United States, international operations generally are subject to extensive government price controls and other market regulations, and increasing emphasis on cost-containment initiatives in the EU, Canada and other countries may put pricing pressure on us. In many countries, the prices of medical products are subject to varying price control mechanisms as part of national health systems. It also can take a significant amount of time after approval of a product to secure pricing and reimbursement for such product in many counties outside the United States. In general, the prices of medicines under such systems are substantially lower than in the United States. Other countries allow companies to fix their own prices for medical products, but monitor and control company profits. Additional foreign price controls or other changes in pricing regulation could restrict the amount that we are able to charge for our product and product candidates. Accordingly, in markets outside the United States, the reimbursement for our products may be reduced compared with the United States and may be insufficient to generate commercially reasonable product revenues.

Moreover, increasing efforts by government and third-party payers in the United States and abroad to cap or reduce healthcare costs may cause such organizations to limit both coverage and the level of reimbursement for new products approved and, as a result, they may not cover or provide adequate payment for our product and product candidates. Payers increasingly are considering new metrics as the basis for reimbursement rates, such as average sale price, average manufacturer price, or AMP, and Actual Acquisition Cost. The existing data for reimbursement based on some of these metrics is relatively limited, although certain states have begun to survey acquisition cost data for the purpose of setting Medicaid reimbursement rates, and CMS has begun making pharmacy National Average Drug Acquisition Cost and National Average Retail Price data publicly available on at least a monthly basis. Therefore, it may be difficult to project the impact of these evolving reimbursement metrics on the willingness of payers to cover any products for which we obtain marketing approval. We expect to experience pricing pressures in connection with the sale of any products for which we obtain marketing approval due to the trend toward managed healthcare, the increasing influence of health maintenance organizations and additional legislative changes. The downward pressure on healthcare costs in general, particularly prescription drugs and surgical procedures and other treatments, has become intense. As a result, increasingly high barriers are being erected to the entry of new products such as ours.

In the EU, each EU Member State may restrict the range of medicinal products for which its national health insurance system provides reimbursement and can control the prices of medicinal products for human use marketed in its territory. As a result, following receipt of marketing authorization in the EU, through any application route, an applicant is required to engage in pricing discussions and negotiations with the competent pricing authority in the individual EU Member States. Some EU Member States operate positive and negative list systems under which products may only be marketed once a reimbursement price has been agreed upon. Other EU Member States approve a specific price for the medicinal product or may instead adopt a system of direct or indirect controls on the profitability of the company placing the medicinal product on the market. The downward pressure on healthcare costs in general, particularly prescription drugs, has become more intense. As a result, increasingly high barriers are being erected to the entry of new products. In addition, we may face competition for our product candidates from lower priced products in foreign countries that have placed price controls on pharmaceutical products.

A health technology assessment, or HTA, of medicinal products is becoming an increasingly common part of the pricing and reimbursement procedures in 24 EU Member States. An HTA is the procedure according to which the assessment of the public health impact, therapeutic impact and the economic and societal impact of use of a given medicinal product in the national healthcare systems of the individual country is conducted. An HTA generally focuses on the clinical efficacy and effectiveness, safety, cost, and cost-effectiveness of individual medicinal products as well as their potential implications for the healthcare system. Those elements of medicinal products are compared with other treatment options available on the market. The outcome of an HTA regarding specific medicinal products will often influence the pricing and reimbursement status granted to these medicinal products by the competent authorities of individual EU Member States. The extent to which pricing and reimbursement decisions are influenced by the HTA of the specific medicinal product varies between EU Member States. In addition, pursuant to Directive 2011/24/EU on the application of patients' rights in cross-border healthcare, a voluntary network of national authorities or bodies responsible for an HTA in the individual EU Member States was established. The purpose of the network is to facilitate and support the exchange of scientific information concerning HTAs. This may lead to harmonization of

the criteria taken into account in the conduct of HTAs between EU Member States and in pricing and reimbursement decisions and may negatively affect price in at least some EU Member States. On January 31, 2018, the European Commission adopted a proposal for a regulation on health technologies assessment. This legislative proposal intends to boost cooperation amongst EU Member States for assessing health technology. If adopted in its current form, the regulation will permit EU Member States to use common HTA tools, methodologies and procedures across the EU, working together in four main areas: joint clinical assessments focusing on the most innovative health technologies with the most potential impact for patients, joint scientific consultations whereby developers can seek advice from HTA authorities, identification of emerging health technologies to identify promising technologies early and continuing voluntary cooperation in other areas.

Table of Contents

Ethical, legal and social issues related to genetic testing may reduce demand for LUXTURNA or any other gene therapy products for which we obtain marketing approval.

We anticipate that prior to receiving certain gene therapies, patients would be required to undergo genetic testing. Genetic testing has raised concerns regarding the appropriate utilization and the confidentiality of information provided by genetic testing. Genetic tests for assessing a person's likelihood of developing a chronic disease have focused public attention on the need to protect the privacy of genetic information. For example, concerns have been expressed that insurance carriers and employers may use these tests to discriminate on the basis of genetic information, resulting in barriers to the acceptance of genetic tests by consumers. This could lead to governmental authorities restricting genetic testing or calling for limits on or regulating the use of genetic testing, particularly for diseases for which there is no known cure. Any of these scenarios could decrease demand for LUXTURNA or any other products for which we obtain marketing approval.

The commercial success of any of our product candidates, if approved, will depend upon its degree of market acceptance by physicians, patients, third-party payers and others in the medical community.

Even with the requisite approvals from FDA in the United States, European Commission in the EU and other regulatory authorities internationally, the commercial success of any products for which we obtain marketing approval will depend, in part, on the acceptance of physicians, patients and health care payers of gene therapy products in general, and our product candidates in particular, as medically necessary, effective, safe, and cost-effective. Any product that we commercialize may not gain acceptance by physicians, patients, health care providers/payers and others in the medical community. If these products do not achieve an adequate level of acceptance, we may not generate significant product revenue and may not become profitable. The degree of market acceptance of gene therapy products of any products for which we obtain marketing approval, will depend on several factors, including:

- the efficacy and safety of such product as demonstrated in clinical trials and subsequently in the market;
- the potential and perceived advantages of such product over alternative treatments;
- the cost of treatment relative to alternative treatments;
- the clinical indications for which such product is approved by FDA or the European Commission;
- patient awareness of, and willingness to seek, genotyping;
- the willingness of physicians to prescribe new therapies;
- the willingness of the target patient population to try new therapies;
- the prevalence and severity of any side effects;
- product labeling requirements imposed by FDA, the European Commission or other regulatory authorities, including any limitations or warnings contained in a product's approved labeling;
- relative convenience and ease of administration;
- the strength of marketing and distribution support;
- the timing of market introduction of competitive products;
- publicity concerning our products or competing products and treatments;
- ethical, social and legal concerns about gene therapy that result in additional regulations restricting or prohibiting our products; and
- sufficient third-party payer coverage and reimbursement.

Even if a potential product displays a favorable benefit/risk profile in clinical trials, market acceptance of the product will not be fully known until after it is launched.

Our gene therapy approach utilizes vectors derived from viruses, which may be perceived as unsafe or may result in unforeseen adverse events. Negative public opinion and increased regulatory scrutiny of gene therapy may damage public perception of the safety of our product and product candidates and adversely affect our ability to conduct our business or obtain regulatory approvals for our product candidates.

Gene therapy remains a novel technology, with no gene therapy product other than LUXTURNA approved for a genetic disease to date in the United States and only two gene therapy products for genetic diseases approved to date in the EU. Public perception may be influenced by claims that gene therapy is unsafe, and gene therapy may not gain the acceptance of the public or the medical community. In particular, our success will depend upon physicians who specialize in the treatment of genetic diseases targeted by our product and product candidates, if approved, prescribing

treatments that involve the use of our product and product candidates, if approved, in lieu of, or in addition to, existing treatments with which they are familiar and for which

Table of Contents

greater clinical data may be available. More restrictive government regulations or negative public opinion would have an adverse effect on our business, financial condition, results of operations and prospects and may delay or impair the development and commercialization of our product candidates or demand for any products we may develop. For example, earlier gene therapy trials led to several well-publicized adverse events, including cases of leukemia and death seen in other trials using other vectors. Serious adverse events in our clinical trials, or other clinical trials involving gene therapy products or our competitors' products, even if not ultimately attributable to the relevant product candidates, and the resulting publicity, could result in increased government regulation, unfavorable public perception, potential regulatory delays in the testing or approval of our product candidates, stricter labeling requirements for those product candidates that are approved and a decrease in demand for LUXTURNA and any other products for which we obtain marketing approval.

If we obtain approval to commercialize any of our product candidates outside of the United States, in particular in the EU, a variety of risks associated with international operations could materially adversely affect our business.

We expect that we will be subject to additional risks in commercializing any of our product candidates outside the United States, including:

- different regulatory requirements for approval of drugs and biologics in foreign countries;
- reduced protection for intellectual property rights;
- unexpected changes in tariffs, trade barriers and regulatory requirements;
- economic weakness, including inflation, or political instability in particular foreign economies and markets;
- compliance with tax, employment, immigration and labor laws for employees living or traveling abroad;
- foreign currency fluctuations, which could result in increased operating expenses and reduced revenues, and other obligations incident to doing business in another country;
- workforce uncertainty in countries where labor unrest is more common than in the United States;
- production shortages resulting from any events affecting raw material supply or manufacturing capabilities abroad; and
- business interruptions resulting from geopolitical actions, including war and terrorism or natural disasters including earthquakes, typhoons, floods and fires.

Risks related to third parties

We have in the past entered, and in the future may enter, into collaborations with third parties to develop or commercialize product candidates. If these collaborations are not successful, our business could be adversely affected.

We have entered into licensing and collaboration agreements with third parties, including our collaboration agreement with Pfizer for the development and commercialization of *SPK-FIX* product candidates and our licensing and commercialization agreement with Novartis for the development and commercialization of voretigene neparvovec outside of the United States. We may enter into additional collaborations in the future. We have limited control over the amount and timing of resources that our collaborators dedicate to the development or commercialization of our product candidates. Our ability to generate revenues from these arrangements will depend on our and our collaborators' abilities to successfully perform the functions assigned to each of us in these arrangements. In addition, our collaborators have the ability to abandon research or development projects and terminate applicable agreements. Moreover, an unsuccessful outcome in any clinical trial for which our collaborator is responsible could be harmful to the public perception and prospects of our gene therapy platform.

Our global collaboration agreement with Pfizer, into which we entered in December 2014, as amended in June 2016 and as further amended in November 2017, relates to the development and commercialization of product candidates for the treatment of hemophilia B. We entered into a supply agreement with Pfizer in February 2018 to supply Pfizer with one batch of *SPK-9001* drug product. In July 2018, we transferred responsibility for our hemophilia B gene therapy program to Pfizer and Pfizer initiated its Phase 3 program.

Our licensing and commercialization agreement with Novartis, into which we entered in January 2018, relates to the development and commercialization of voretigene neparvovec outside of the United States. Under this agreement, we granted Novartis an exclusive right and license for the development and commercialization of voretigene neparvovec in humans outside of the United States. We retain responsibility for maintaining marketing authorization for

LUXTURNA granted by the European Commission, and Novartis is responsible for seeking regulatory approval for voretigene neparvovec outside of the United States and EU. If Novartis fails to devote sufficient financial and other resources to the future development and commercialization of voretigene neparvovec outside the United States, the development and commercialization of voretigene neparvovec outside of the United States could be delayed or could fail, which would result in a delay of receiving milestone payments or royalties with respect to voretigene neparvovec or in our not receiving milestone payments or royalties at all. Novartis has the right to terminate the license agreement at any time upon one year's prior written notice to us. Novartis also

Table of Contents

may terminate the license agreement in the event there is an uncured material breach of our supply agreement by us, resulting in Novartis taking over manufacturing of voretigene neparvovec, or in the event we undergo a change of control. In addition, if Novartis takes over manufacturing of voretigene neparvovec because of our uncured material breach of the supply agreement, the royalties we receive under the license agreement will be reduced. If Novartis terminates our agreement at any time, because of an uncured material breach of the supply agreement or for any other reason, it would delay or prevent our further development and commercialization of voretigene neparvovec, may materially harm our business and could accelerate our need for additional capital.

We may enter into additional collaborations with third parties in the future. Our relationships with third parties, including Pfizer and Novartis, and any future collaborations we enter in the future, may pose several risks, including the following:

- collaborators have significant discretion in determining the efforts and resources that they will apply to these collaborations;
- collaborators may not perform their obligations as expected;
- we may not achieve any milestones, or receive any milestone payments, under our collaborations, including milestones and/or payments that we expect to achieve or receive;
- our collaborators may not achieve sales targets and we may not receive significant royalty payments based on sales by our collaborators;
- the clinical trials conducted as part of these collaborations may not be successful;
- collaborators may not pursue development and commercialization of any product candidates that achieve regulatory approval or may elect not to continue or renew development or commercialization programs based on clinical trial results, changes in the collaborators' strategic focus or available funding or external factors, such as an acquisition, that divert resources or create competing priorities;
- collaborators may delay clinical trials, provide insufficient funding for clinical trials, stop a clinical trial or abandon a product candidate, repeat or conduct new clinical trials or require a new formulation of a product candidate for clinical testing;
- we may not have access to, or may be restricted from disclosing, certain information regarding product candidates being developed or commercialized under a collaboration and, consequently, may have limited ability to inform our stockholders about the status of such product candidates;
- collaborators could independently develop, or develop with third parties, products that compete directly or indirectly with our product candidates if the collaborators believe that competitive products are more likely to be successfully developed or can be commercialized under terms that are more economically attractive than ours;
- product candidates developed in collaboration with us may be viewed by our collaborators as competitive with their own product candidates or products, which may cause collaborators to cease to devote resources to the commercialization of our product candidates;
- a collaborator with marketing and distribution rights to one or more of our product candidates that achieve regulatory approval may not commit sufficient resources to the marketing and distribution of any such product candidate;
- disagreements with collaborators, including disagreements over proprietary rights, contract interpretation or the preferred course of development of any product candidates, may cause delays or termination of the research, development or commercialization of such product candidates, may lead to additional responsibilities for us with respect to such product candidates or may result in litigation or arbitration, any of which would be time-consuming and expensive;
- collaborators may not properly maintain or defend our intellectual property rights or may use our proprietary information in such a way as to invite litigation that could jeopardize or invalidate our intellectual property or proprietary information or expose us to potential litigation;
- disputes may arise with respect to the ownership of intellectual property developed pursuant to our collaborations;
- collaborators may infringe the intellectual property rights of third parties, which may expose us to litigation and potential liability; and
- collaborations may be terminated for the convenience of the collaborator and, if terminated, we could be required to raise additional capital to pursue further development or commercialization of the applicable product candidates.

54

Table of Contents

If our collaborations do not result in the successful development and commercialization of products, or if one of our collaborators terminates its agreement with us, we may not receive any future research funding or milestone or royalty payments under the collaboration. If we do not receive the funding we expect under these agreements, our development of product candidates could be delayed, and we may need additional resources to develop our product candidates. In addition, if one of our collaborators terminates its agreement with us, we may find it more difficult to attract new collaborators and the perception of us in the business and financial communities could be adversely affected. Our collaborators are subject to similar risks with respect to product development, regulatory approval and commercialization and their business, results of operations and financial condition could be harmed should they experience any such risks, which could adversely affect our collaboration.

We may in the future decide to collaborate with pharmaceutical and biotechnology companies for the development and potential commercialization of our product candidates. These relationships, or those like them, may require us to incur non-recurring and other charges, increase our near- and long-term expenditures, issue securities that dilute our existing stockholders or disrupt our management and business. In addition, we could face significant competition in seeking appropriate collaborators and the negotiation process is time-consuming and complex. Our ability to reach a definitive collaboration agreement will depend, among other things, upon our assessment of the collaborator's resources and expertise, the terms and conditions of the proposed collaboration and the proposed collaborator's evaluation of several factors. If we license rights to product candidates, we may not be able to realize the benefit of such transactions if we are unable to successfully integrate them with our existing operations and company culture.

We may not be successful in finding strategic collaborators for continuing development of certain of our product candidates or successfully commercializing or competing in the market for certain indications.

We may seek to develop strategic partnerships for developing certain of our product candidates or commercializing certain of our products and product candidates, due to capital costs required to develop the product candidates or manufacturing constraints. We may not be successful in our efforts to establish such a strategic partnership or other alternative arrangements for our products or product candidates because our research and development pipeline may be insufficient, our product candidates may be deemed to be at too early of a stage of development for collaborative effort or third parties may not view our product candidates as having the requisite potential to demonstrate safety and efficacy. In addition, we may be restricted under existing collaboration agreements from entering into future agreements with potential collaborators. For example, under our collaboration with Pfizer, we are subject to certain restrictions on our ability to directly or indirectly engage in certain activities relating to competing factor IX gene therapy products. We cannot be certain that, following a strategic transaction or license, we will achieve an economic benefit that justifies such transaction.

If we are unable to reach agreements with suitable collaborators on a timely basis, on acceptable terms or at all, we may have to curtail the development of a product candidate, reduce or delay its development program, delay its potential commercialization, reduce the scope of any sales or marketing activities or increase our expenditures and undertake development or commercialization activities at our own expense. If we elect to fund development or commercialization activities on our own, we may need to obtain additional expertise and additional capital, which may not be available to us on acceptable terms or at all. If we fail to enter into collaborations and do not have sufficient funds or expertise to undertake the necessary development and commercialization activities, we may not be able to further develop our product candidates and our business, financial condition, results of operations and prospects may be materially and adversely affected.

Risks related to manufacturing

Gene therapies are novel, complex and difficult to manufacture. We could experience production problems in our network of internal and external (CDMO) facilities that result in delays in our development or commercialization programs or otherwise adversely affect our business.

We completed construction of our own manufacturing facility in 2014, and we may encounter difficulties in operating this facility. The manufacturing process we use to produce LUXTURNA and our product candidates is complex, novel and has been validated for commercial use only with respect to LUXTURNA in the United States and in Europe. Several factors could cause production interruptions, including equipment malfunctions, facility contamination, raw material shortages or contamination, natural disasters, disruption in utility services, human error or

disruptions in the operations of our suppliers.

Our product and product candidates require processing steps that are more complex than those required for most chemical pharmaceuticals. Moreover, unlike chemical pharmaceuticals, the physical and chemical properties of a biologic such as ours generally cannot be fully characterized. As a result, assays of the finished product may not be sufficient to ensure that the product will perform in the intended manner. Accordingly, we employ multiple steps to control our manufacturing process to assure that the product or product candidate is made strictly and consistently in compliance with the process. Problems with the manufacturing process, even minor deviations from the normal process, could result in product defects or manufacturing failures that result in lot failures, product recalls, product liability claims or insufficient inventory. We may encounter problems achieving adequate quantities and quality of clinical-grade materials that meet FDA, EU or other applicable standards or specifications with consistent and acceptable production yields and costs.

Table of Contents

In addition, FDA, EMA and other foreign regulatory authorities may require us to submit samples of any lot of any approved product together with the protocols showing the results of applicable tests at any time. Under some circumstances, FDA, EMA or other foreign regulatory authorities may require that we not distribute a lot until the agency authorizes its release. Slight deviations in the manufacturing process, including those affecting quality attributes and stability, may result in unacceptable changes in the product that could result in lot failures or product recalls. We have experienced lot failures in the past and there is no assurance we will not experience such failures in the future. Lot failures or product recalls could cause us to delay product launches or clinical trials, which could be costly to us and otherwise harm our business, financial condition, results of operations and prospects.

We also may encounter problems hiring and retaining the experienced specialist scientific, quality control and manufacturing personnel needed to operate our manufacturing process, which could result in delays in our production or difficulties in maintaining compliance with applicable regulatory requirements.

Any problems in our manufacturing process or facilities could make us a less attractive collaborator for potential partners, including larger pharmaceutical companies and academic research institutions, which could limit our access to additional attractive development programs. Problems in our manufacturing process or CDMO facilities also could restrict our ability to meet market demand for LUXTURNA, or any product candidates for which we may receive marketing approval, and to meet our supply obligations to Novartis. Under our supply agreement with Novartis, we have agreed to provide all of the commercial supply of LUXTURNA required by Novartis, subject to certain conditions. If we are unable to produce enough product to meet the required demand, or if the product we produce does not satisfy the quality standards set forth in the supply agreement, Novartis may be able to manufacture LUXTURNA, terminate our license agreement and/or pay reduced royalties on LUXTURNA. While we have manufactured sufficient supplies for the commercial launch of LUXTURNA in the United States, we may not be able to manufacture sufficient supplies to continue commercial sales on a long-term basis.

Disruptions in our manufacturing process may delay or disrupt our commercialization efforts.

Our GMP manufacturing facility was approved by FDA for the commercial manufacture of LUXTURNA in December 2017 and by EMA in 2018. As an approved facility, we will need to continue to ensure that all of our processes, methods and equipment are compliant with cGMP and perform extensive audits of vendors, contract laboratories and suppliers. If any of our vendors, contract laboratories or suppliers is found to be out of compliance with cGMP, we may experience delays or disruptions in manufacturing while we work with these third parties to remedy the violation or while we work to identify suitable replacement vendors, contract laboratories or suppliers. The cGMP requirements govern quality control of the manufacturing process and documentation policies and procedures. In complying with cGMP, we will be obligated to expend time, money and effort in production, record keeping and quality control to assure that the product meets applicable specifications and other requirements. If we fail to comply with these requirements, we would be subject to possible regulatory action and may not be permitted to sell any products that we may develop.

We may rely on third parties to conduct aspects of our product manufacturing, and these third parties may not perform satisfactorily.

While we produce our commercial supply of LUXTURNA at our own facility, we may rely on third parties for the production of certain materials for our product candidates and, therefore, we can control only certain aspects of their activities. We have manufacturing agreements with third parties that provide for, among other things, production of product candidates for our current and future early stage clinical trials. Under certain circumstances, the other party is entitled to terminate its arrangement with us. If we need to enter into alternative arrangements, it could delay our product development activities. Our reliance on third parties for certain manufacturing activities will reduce our control over these activities but will not relieve us of our responsibility to ensure compliance with all required regulations. If a third party does not successfully carry out its contractual duties, meet expected deadlines or manufacture our product candidates in accordance with regulatory requirements, or if there are disagreements between us and any such third party, we will not be able to complete, or may be delayed in completing, the preclinical studies required to support future IND submissions and the clinical trials required for approval of our product candidates. In such instances, we may need to enter into an appropriate replacement third-party relationship, which may not be readily available or on acceptable terms, which would cause additional delay or increased expense prior to the

approval of our product candidates and would thereby have a material adverse effect on our business, financial condition, results of operations and prospects.

Our reliance on these third parties entails risks to which we would not be subject if we manufactured the product candidates ourselves, including:

- reduced control for certain aspects of manufacturing activities;
- termination or nonrenewal of manufacturing and service agreements with third parties in a manner or at a time that is costly or damaging to us; and

Table of Contents

- disruptions to the operations of our third-party manufacturers and service providers caused by conditions unrelated to our business or operations, including the bankruptcy of the manufacturer or service provider.

Any of these events could lead to clinical trial delays or failure to obtain regulatory approval, or impact our ability to successfully commercialize future product candidates. Some of these events could be the basis for FDA action or action of equivalent competent authorities in foreign jurisdictions, including injunction, recall, seizure or total or partial suspension of product manufacture.

Failure to comply with ongoing regulatory requirements could cause us to suspend production or put in place costly or time-consuming remedial measures.

The regulatory authorities may, at any time following approval of a product for sale, audit the manufacturing facilities for such product. If any such inspection or audit identifies a failure to comply with applicable regulations, or if a violation of product specifications or applicable regulations occurs independent of such an inspection or audit, the relevant regulatory authority may require remedial measures that may be costly or time-consuming to implement and that may include the temporary or permanent suspension of a clinical trial or commercial sales or the temporary or permanent closure of a manufacturing facility. Any such remedial measures imposed upon us could materially harm our business, financial condition, results of operations and prospects.

If we fail to comply with applicable cGMP regulations, FDA and foreign regulatory authorities can impose regulatory sanctions including, among other things, refusal to approve a pending application for a new product candidate or suspension or revocation of a pre-existing approval. Such an occurrence may cause our business, financial condition, results of operations and prospects to be materially harmed.

Additionally, if supply from our facility is interrupted, there could be a significant disruption in commercial supply of LUXTURNA or any other product for which we obtain marketing approval, and in clinical supply for our product candidates. This also could affect our ability to meet our supply obligations under our agreement with Novartis. We currently do not have a backup manufacturer for commercial supply of LUXTURNA and have limited back-up manufacturing capacity for clinical trial supply for our product candidates. An alternative manufacturer would need to be qualified, through regulatory filings, which could result in further delay. The regulatory authorities also may require additional clinical trials if a new manufacturer is relied upon for commercial production. Switching manufacturers may involve substantial costs and could result in a delay in our desired clinical and commercial timelines.

Our reliance on third parties requires us to share our trade secrets, which increases the possibility that a competitor will discover them or that our trade secrets will be misappropriated or disclosed.

Because we currently rely on third parties to manufacture certain of our product candidates and to perform quality testing, and because we collaborate with various organizations and academic institutions for the advancement of our gene therapy platform, we must, at times, share our proprietary technology and confidential information, including trade secrets, with them. We seek to protect our proprietary technology, in part, by entering into confidentiality agreements and, if applicable, material transfer agreements, collaborative research agreements, consulting agreements or other similar agreements with our collaborators, advisors, employees and consultants prior to beginning research or disclosing proprietary information. These agreements typically limit the rights of the third parties to use or disclose our confidential information. Despite the contractual provisions employed when working with third parties, the need to share trade secrets and other confidential information increases the risk that such trade secrets become known by our competitors, are inadvertently incorporated into the technology of others or are disclosed or used in violation of these agreements. Given that our proprietary position is based, in part, on our know-how and trade secrets, a competitor’s discovery of our proprietary technology and confidential information or other unauthorized use or disclosure would impair our competitive position and may have a material adverse effect on our business, financial condition, results of operations and prospects.

Despite our efforts to protect our trade secrets, our competitors may discover our trade secrets, either through breach of these agreements, independent development or publication of information including our trade secrets by third parties. A competitor’s discovery of our trade secrets would impair our competitive position and have an adverse impact on our business, financial condition, results of operations and prospects.

Any contamination in our manufacturing process, shortages of raw materials or failure of any of our key suppliers to deliver necessary components could result in delays in our clinical development or marketing schedules and adversely affect our ability to meet our supply obligations to Novartis.

Given the nature of biologics manufacturing, there is a risk of contamination. Any contamination could materially adversely affect our ability to produce product candidates on schedule and could, therefore, harm our results of operations and cause reputational damage.

Table of Contents

Some of the raw materials and other components required in our manufacturing process are derived from biologic sources. Such raw materials are difficult to procure and may be subject to contamination or recall. A material shortage, contamination, recall or restriction on the use of biologically derived substances in the manufacture of our product or product candidates could adversely impact or disrupt the commercial manufacturing or the production of clinical material, which could materially and adversely affect our development and commercialization timelines and our business, financial condition, results of operations and prospects and could adversely affect our ability to meet our supply obligations to Novartis.

Interruptions in the supply of product or inventory loss may adversely affect our operating results and financial condition.

LUXTURNA and our product candidates are manufactured using technically complex processes requiring specialized facilities, highly specific raw materials and other production constraints. The complexity of these processes, as well as strict government standards for the manufacture and storage of our products, subjects us to production risks. While product batches released for use in clinical trials or for commercialization undergo sample testing, some defects may only be identified following product release. In addition, process deviations or unanticipated effects of approved process changes may result in these intermediate products not complying with stability requirements or specifications. Our product and product candidates must be stored and transported at temperatures within a certain range. If these environmental conditions deviate, our product's and product candidates' remaining shelf-lives could be impaired or their efficacy and safety could be adversely affected, making them no longer suitable for use.

The occurrence, or suspected occurrence, of production and distribution difficulties can lead to lost inventories and, in some cases, product recalls, with consequential reputational damage and the risk of product liability. The investigation and remediation of any identified problems can cause production delays, substantial expense, lost sales and delays of new product launches. Any interruption in the supply of finished products or the loss thereof could hinder our ability to timely distribute our products and satisfy customer demand. Any unforeseen failure in the storage of the product or loss in supply could delay our clinical trials and, with respect to LUXTURNA or any of our product candidates that may be approved, result in a loss of our market share and negatively affect our business, financial condition, results of operations and prospects.

Risks related to our business operations

We may not be successful in our efforts to identify or discover additional product candidates and may fail to capitalize on programs or product candidates that may be a greater commercial opportunity or for which there is a greater likelihood of success.

The success of our business depends upon our ability to identify, develop and commercialize product candidates based on our gene therapy platform. Research programs to identify new product candidates require substantial technical, financial and human resources. Although certain of our product candidates are currently in clinical or preclinical development, we may fail to identify other potential product candidates for clinical development for several reasons. For example, our research may be unsuccessful in identifying potential product candidates or our potential product candidates may be shown to have harmful side effects, may be commercially impracticable to manufacture or may have other characteristics that may make the products unmarketable or unlikely to receive marketing approval. Additionally, because we have limited resources, we may forego or delay pursuit of opportunities with certain programs or product candidates or for indications that later prove to have greater commercial potential. Our spending on current and future research and development programs may not yield any commercially viable products. If we do not accurately evaluate the commercial potential for a particular product candidate, we may relinquish valuable rights to that product candidate through strategic collaboration, licensing or other arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights to such product candidate. Alternatively, we may allocate internal resources to a product candidate in a therapeutic area in which it would have been more advantageous to enter into a partnering arrangement.

If any of these events occur, we may be forced to abandon our development efforts with respect to a particular product candidate or fail to develop a potentially successful product candidate, which could have a material adverse effect on our business, financial condition, results of operations and prospects.

Our future success depends on our ability to retain key employees and to attract, retain and motivate qualified personnel.

We are dependent on members of our executive team, the loss of whose services may adversely impact the achievement of our objectives. While we have entered into employment agreements with each of our executive officers, any of them could leave our employment at any time, as all of our employees are "at will" employees. We do not have "key person" insurance on any of our employees. The loss of the services of one or more of our current employees might impede the achievement of our research, development and commercialization objectives. Recruiting and retaining other qualified employees for our business, including scientific and technical personnel is, and will continue to be, critical to our success. There currently is a shortage of skilled individuals with substantial gene therapy experience, which is likely to continue. As a result, competition for skilled personnel, including in gene therapy research and

Table of Contents

vector manufacturing, is intense and the turnover rate can be high. We may not be able to attract and retain personnel on acceptable terms given the competition among numerous pharmaceutical and biotechnology companies and academic institutions for individuals with similar skill sets. In addition, failure to succeed in preclinical or clinical trials or applications for marketing approval may make it more challenging to recruit and retain qualified personnel. The inability to recruit, or loss of services of certain executives or key employees, may impede the progress of our research, development and commercialization objectives and have a material adverse effect on our business, financial condition, results of operations and prospects.

If we are unable to manage expected growth in the scale and complexity of our operations, our performance may suffer.

If we are successful in executing our business strategy, we will need to expand our managerial, operational, financial and other systems and resources in connection with the commercialization of LUXTURNA in the United States as well as to manage our operations, continue our research and development activities and, over the longer term, continue to build a commercial infrastructure to support commercialization of any other products for which we obtain marketing approval. Future growth would impose significant added responsibilities on members of management. It is likely that our management, finance, development personnel, systems and facilities currently in place may not be adequate to support this future growth. Our need to effectively manage our operations, growth and product candidates and the commercialization of LUXTURNA requires that we continue to develop more robust business processes and improve our systems and procedures in each of these areas and to attract and retain sufficient numbers of talented employees. We may be unable to successfully implement these tasks on a larger scale and, accordingly, may not achieve our research, development, commercialization and growth goals.

Our employees, principal investigators, consultants, advisors and commercial partners may engage in misconduct or other improper activities, including non-compliance with regulatory standards and requirements and insider trading.

We are exposed to the risk of fraud or other misconduct by our employees, principal investigators, consultants, advisors and commercial partners. Misconduct by these parties could include intentional failures to comply with FDA regulations or the regulations applicable in the EU and other jurisdictions, provide accurate information to FDA, the European Commission and other regulatory authorities, comply with healthcare fraud and abuse laws and regulations in the United States and abroad, report financial information or data accurately or disclose unauthorized activities to us. In particular, sales, marketing and business arrangements in the healthcare industry are subject to extensive laws and regulations intended to prevent fraud, misconduct, kickbacks, self-dealing and other abusive practices. These laws and regulations restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales commission, customer incentive programs and other business arrangements. Such misconduct also could involve the improper use of information obtained in the course of clinical trials or interactions with FDA or other regulatory authorities, which could result in regulatory sanctions and cause serious harm to our reputation. We have adopted a code of conduct applicable to all of our employees, but it is not always possible to identify and deter employee misconduct, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from government investigations or other actions or lawsuits stemming from a failure to comply with these laws or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, financial condition, results of operations and prospects, including the imposition of significant fines or other sanctions.

Healthcare legislative and regulatory reform measures may have a material adverse effect on our business and results of operations.

Our industry is highly regulated and changes in law may adversely impact our business, operations or financial results. The Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, or the PPACA, is a sweeping measure intended to, among other things, expand healthcare coverage within the United States, primarily through the imposition of health insurance mandates on employers and individuals and expansion of the Medicaid program.

Several provisions of the law may affect us and increase certain of our costs. See the risk factor entitled "*Failure to comply with reporting and payment obligations under the Medicaid Drug Rebate program or other governmental*

pricing programs could result in additional reimbursement requirements, penalties, sanctions and fines which could have a material adverse effect on our business, financial condition, results of operations and growth prospects" for more information regarding PPACA.

In addition, other legislative changes have been adopted since the PPACA was enacted. These changes include aggregate reductions in Medicare payments to providers of 2% per fiscal year, which went into effect on April 1, 2013 and, following passage of the Bipartisan Budget Act of 2018, will remain in effect through 2027 unless additional Congressional action is taken. In January 2013, President Obama signed into law the American Taxpayer Relief Act of 2012, which, among other things, further reduced Medicare payments to several types of providers and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. These laws may result in additional reductions in

Table of Contents

Medicare and other healthcare funding, which could have a material adverse effect on our customers and, accordingly, our financial operations.

We anticipate that the PPACA, as well as other healthcare reform measures that may be adopted in the future, may result in more rigorous coverage criteria and an additional downward pressure on the reimbursement our customers may receive for our products. Further, there have been, and there may continue to be, judicial and Congressional challenges to certain aspects of the PPACA. For example, the U.S. Tax Cuts and Jobs Act of 2017 includes a provision repealing, effective January 1, 2019, the tax-based shared responsibility payment imposed by the Affordable Care Act on certain individuals who fail to maintain qualifying health coverage for all or part of a year that is commonly referred to as the "individual mandate". Additional legislative and regulatory changes to the PPACA, its implementing regulations and guidance and its policies, remain possible in the 115th U.S. Congress and under the Trump Administration. However, it remains unclear how any new legislation or regulation might affect the prices we may obtain for LUXTURNA or any of our product candidates for which regulatory approval is obtained. Any reduction in reimbursement from Medicare and other government programs may result in a similar reduction in payments from private payers. The implementation of cost containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain profitability or commercialize our products.

We may be subject, directly or indirectly, to federal and state healthcare fraud and abuse laws, false claims laws and health information privacy and security laws. If we are unable to comply, or have not fully complied, with such laws, we could face substantial penalties.

In the United States, the research, manufacturing, distribution, sale, and promotion of drugs and biologic products are subject to regulation by various federal, state, and local authorities in addition to FDA, including CMS, other divisions of the United States Department of Health and Human Services, or HHS, (e.g., the Office of Inspector General), the United States Department of Justice offices of the United States Attorney, the Federal Trade Commission and state and local governments. Our operations are directly, or indirectly through our prescribers, customers and purchasers, subject to various federal and state fraud and abuse laws and regulations, including, without limitation, the federal Anti-Kickback Statute, the federal civil and criminal False Claims Act and Physician Payments Sunshine Act and regulations and equivalent provisions in other countries. These laws apply to, among other things, our proposed sales, marketing and educational programs. In addition, we may be subject to patient privacy laws by both the federal government and the states in which we conduct our business. The laws that affect our operations include, but are not limited to:

- the federal Anti-Kickback Statute, which prohibits, among other things, persons or entities from knowingly and willfully soliciting, receiving, offering or paying any remuneration (including any kickback, bribe or rebate), directly or indirectly, overtly or covertly, in cash or in kind, in return for the purchase, recommendation, leasing or furnishing of an item or service reimbursable under a federal healthcare program, such as the Medicare and Medicaid programs. This statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on the one hand, and prescribers, purchasers and formulary managers on the other. Liability may be established under the federal Anti-Kickback Statute without proving actual knowledge of the statute or specific intent to violate it. There are a number of statutory exemptions and regulatory safe harbors protecting some common activities from prosecution; however, those exceptions and safe harbors are drawn narrowly. Failure to meet all of the requirements of a particular statutory exception or regulatory safe harbor does not make the conduct per se illegal under the Anti-Kickback Statute, but the legality of the arrangement will be evaluated on a case-by-case basis based on the totality of the facts and circumstances. We seek to comply with the exemptions and safe harbors whenever possible, but our practices may not in all cases meet all of the criteria for safe harbor protection from anti-kickback liability. Moreover, there are no safe harbors for many common practices, such as educational and research grants or patient assistance programs. Violations of the Anti-Kickback Statute are subject to significant civil, criminal, and administrative penalties, including damages, fines, imprisonment, and exclusion from government-funded healthcare programs like Medicare and Medicaid;
- the federal civil False Claims Act, which prohibits any person from knowingly presenting, or causing to be presented, a false or fraudulent claim for payment of government funds; or knowingly and improperly avoiding, decreasing, or concealing an obligation to pay money to the federal government. In recent years,

several pharmaceutical and other healthcare companies have faced enforcement actions under the federal False Claims Act for allegedly submitting false or misleading pricing information to government health care programs and providing free product to customers with the expectation that the customers would bill federal programs for the product. Other companies have faced enforcement actions for causing false claims to be submitted because of the company marketing a product for unapproved, and thus non-reimbursable, uses. In addition, the government may assert that a claim including items or services resulting from a violation of the federal anti-kickback statute constitutes a false or fraudulent claim for purposes of the federal civil False Claims Act. The civil False Claims Act also permits an individual acting as a “whistleblower” to bring actions on behalf of the federal government alleging violations of the statute and to share in any monetary recovery. False Claims Act liability is potentially significant because the statute provides for trebling of

Table of Contents

proved sustained damages and significant mandatory penalties per false claim. Because of the potential for large monetary exposure, healthcare and pharmaceutical companies often resolve allegations without admissions of liability for significant and material amounts to avoid the uncertainty of treble damages and per claim penalties that may awarded in litigation proceedings. Companies may be required, however, to enter into corporate integrity agreements with the government, which may impose substantial costs on companies to ensure compliance. Criminal prosecution is possible for making or presenting a false or fictitious or fraudulent claim to the federal government;

- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which imposes criminal and civil liability for, among, other things, executing, or attempting to execute, a scheme to defraud any healthcare benefit program or knowingly and willfully falsifying, concealing, or covering up a material fact or making any materially false, fictitious, or fraudulent statement or representation, or making or using any false writing or document knowing the same to contain any materially false, fictitious or fraudulent statement or entry, in connection with the delivery of, or payment for, healthcare benefits, items, or services;
- HIPAA and its implementing regulations, which impose certain requirements relating to the privacy, security and transmission of individually identifiable health information without appropriate authorization by entities subject to the rule, such as health plans, health care clearinghouses and health care providers;
- numerous other federal and state laws and regulations that address privacy and data security, including state data breach notification laws, state health information privacy laws, and federal and state consumer protection laws (e.g., Section 5 of the Federal Trade Commission Act, or FTC Act), govern the collection, use, disclosure and protection of health-related and other personal information, many of which differ from each other in significant ways, thus complicating compliance efforts;
- the federal Physician Payment Sunshine Act, being implemented as the Open Payments Program, imposes annual reporting requirements on certain manufacturers of drugs, devices, or biologics for payments and other transfers of value, directly or indirectly, to physicians and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members. A manufacturer's failure to submit timely, accurately and completely the required information for all payments, transfers of value or ownership or investment interests may result in civil monetary penalties of up to an aggregate of $150,000 per year, and up to an aggregate of $1 million per year for "knowing failures." Manufacturers must submit reports by the 90th day of each calendar year; and
- analogous state laws and regulations, such as state anti-kickback and false claims laws, and state fair trade practices laws may apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by non-governmental third-party payers, including private insurers. Several states also require pharmaceutical companies to report expenses relating to the marketing and promotion of pharmaceutical products in those states and to report gifts and payments to individual health care providers in those states. Some of these states also prohibit certain marketing-related activities, including the provision of gifts, meals, or other items to certain health care providers. Other states have laws requiring pharmaceutical sales representatives to be registered or licensed, and still others impose limits on co-pay assistance that pharmaceutical companies can offer to patients. In addition, several states require pharmaceutical companies to implement compliance programs or marketing codes.

State and federal regulatory and enforcement agencies continue actively to investigate violations of health care laws and regulations, and the United States Congress continues to strengthen the arsenal of enforcement tools. Most recently, the Bipartisan Budget Act of 2018 increased the criminal and civil penalties that can be imposed for violating certain federal health care laws, including the Anti-Kickback Statute. Enforcement agencies also continue to pursue novel theories of liability under these laws. Government agencies have recently increased regulatory scrutiny and enforcement activity with respect to programs supported or sponsored by pharmaceutical companies, including reimbursement and co-pay support, funding of independent charitable foundations and other programs that offer benefits for patients. Several investigations into these programs have resulted in significant civil and criminal settlements.

Because of the breadth of these laws and the narrowness of the statutory exceptions and safe harbors available, it is possible that some of our business activities could be subject to challenge under one or more of such laws. If our operations are found to be in violation of any of the laws described above or any other government regulations that apply to us, we may be subject to penalties, including civil and criminal penalties, damages, fines, exclusion from

participation in government health care programs, such as Medicare and Medicaid, imprisonment and the curtailment or restructuring of our operations, any of which could adversely affect our ability to operate our business and our results of operations. Even if we are not determined to have violated these laws, government investigations into these issues typically require the expenditure of significant resources and generate negative publicity, which could harm our financial condition and divert the attention of our management from operating our business.

In the EU, interactions between pharmaceutical companies and physicians are also governed by strict laws, regulations, industry self-regulation codes of conduct and physicians' codes of professional conduct in the individual EU Member States.

Table of Contents

The provision of benefits or advantages to physicians to induce or encourage the prescription, recommendation, endorsement, purchase, supply, order or use of medicinal products is prohibited in the EU. The provision of benefits or advantages to physicians is also governed by the national anti-bribery laws of EU Member States, such as the UK Bribery Act 2010. The UK Bribery Act applies to any company incorporated in or "carrying on business" in the UK, irrespective of where in the world the alleged bribery activity occurs, which could have implications for our interactions with physicians both in and outside of the UK. Infringement of these laws could result in substantial fines and imprisonment.

Payments made to physicians in certain EU Member States must be publicly disclosed. Moreover, agreements with physicians often must be the subject of prior notification and approval by the physician's employer, his or her competent professional organization and/or the regulatory authorities of the individual EU Member States. These requirements are provided in the national laws, industry codes or professional codes of conduct, applicable in the EU Member States. Failure to comply with these requirements could result in reputational risk, public reprimands, administrative penalties, fines or imprisonment.

EU Member States, Switzerland and other countries have also adopted data protection laws and regulations, which impose significant compliance obligations. In the EU, the collection and use of personal health data is currently governed by the provisions of the General Data Protection Regulation, or the GDPR. The GDPR went into effect on May 25, 2018, repealing the Data Protection Directive and increasing our responsibility and liability in relation to the processing of personal data of EU subjects. The GDPR, together with the national legislation of the individual EU Member States governing the processing of personal data, impose strict obligations and restrictions on the ability to collect, analyze and transfer personal data, including health data from clinical trials and adverse event reporting. In particular, these obligations and restrictions concern the consent of the individuals to whom the personal data relates, the information provided to the individuals for the consent to be considered valid, the transfer of personal data out of the EU, security breach notifications, the use of third-party processors in connection with the processing of the personal data, confidentiality of the personal data, as well as substantial potential fines for breaches of the data protection obligations. Data protection authorities from the different EU Member States may interpret the GDPR and national laws differently and impose additional requirements, which add to the complexity of processing personal data in the EU.

Guidance on implementation and compliance practices are often updated or otherwise revised. With respect to the transfer of personal data out of the EU, the GDPR provides that the transfer of personal data to countries outside of the European Economic Area that are not considered by the European Commission to provide an adequate level of data protection, including the United States, is permitted only on the basis of specific legal grounds.

The judgment by the Court of Justice of the EU in the Schrems case (Case C-362/14 Maximillian Schrems v. Data Protection Commissioner) determined the safe harbor framework, which was relied upon by many United States entities as a basis for transfer of personal data from the EU to the United States, to be invalid. United States entities therefore, had only the possibility to rely on the alternate procedures for such data transfer provided in the EU Data Protection Directive.

On February 29, 2016, however, the European Commission announced an agreement with the United States Department of Commerce, or the DOC, to replace the invalidated safe harbor framework with a new "Privacy Shield". On July 12, 2016, the European Commission adopted a decision on the adequacy of the protection provided by the Privacy Shield. The Privacy Shield is intended to address the requirements set out by the Court of Justice of the European Union in its Schrems judgment by imposing more stringent obligations on companies, providing stronger monitoring and enforcement by the DOC and the Federal Trade Commission, and making commitments on the part of public authorities regarding access to information. United States entities have been able to certify to the DOC their compliance with the privacy principles of the Privacy Shield since August 1, 2016 and rely on the Privacy Shield certification to transfer personal data from the EU to the United States.

In October 2016, an action for annulment was brought by three French digital rights advocacy group, La Quadrature du Net, French Data Network and the Fédération FDN (Case T-738/16). The case currently is pending before the Court of Justice of the EU. If the Court of Justice of the EU invalidates the Privacy Shield, it will no longer be possible to rely on the Privacy Shield certification to transfer personal data from the EU to entities in the United

States. Adherence to the Privacy Shield is not, however, mandatory. Entities based in the United States are permitted to rely either on their adherence to the Privacy Shield or on the other authorized means and procedures to transfer personal data provided by the GDPR.

To comply with the new data protection rules imposed by the GDPR, we are required to put in place additional mechanisms ensuring compliance. This may be onerous and adversely affect our business, financial condition, results of operations and prospects.

If we fail to comply with data protection laws and regulations, we could be subject to government enforcement actions (which could include civil or criminal penalties), private litigation and/or adverse publicity, which could negatively affect our operating results and business.

Table of Contents

We may be subject to data protection laws and regulations (i.e., laws and regulations that address privacy and data security). In the United States, numerous federal and state laws and regulations, including state data breach notification laws, state health information privacy laws, and federal and state consumer protection laws (e.g., Section 5 of the FTC Act and HIPAA), govern the collection, use, disclosure, and protection of health-related and other personal information. Failure to comply with data protection laws and regulations could result in government enforcement actions and create liability for us (which could include civil and/or criminal penalties), private litigation and/or adverse publicity that could negatively affect our operating results and business.

The collection, use, disclosure, transfer, or other processing of personal data regarding individuals in the EU, including personal health data, is subject to the GDPR, which became effective on May 25, 2018. The GDPR is wide-ranging in scope and imposes numerous requirements on companies that process personal data, including requirements relating to processing health and other sensitive data, obtaining consent of the individuals to whom the personal data relates, providing information to individuals regarding data processing activities, implementing safeguards to protect the security and confidentiality of personal data, providing notification of data breaches, and taking certain measures when engaging third-party processors. The GDPR also imposes strict rules on the transfer of personal data to countries outside the EU, including the United States, and permits data protection authorities to impose large penalties for violations of the GDPR, including potential fines of up to €20 million or 4% of annual global revenues, whichever is greater. The GDPR also confers a private right of action on data subjects and consumer associations to lodge complaints with supervisory authorities, seek judicial remedies, and obtain compensation for damages resulting from violations of the GDPR. Compliance with the GDPR is a rigorous and time-intensive process that may increase our cost of doing business or require us to change our business practices, and despite those efforts, there is a risk that we may be subject to fines and penalties, litigation, and reputational harm in connection with any activities falling within the scope of the GDPR.

Failure to comply with reporting and payment obligations under the Medicaid Drug Rebate program or other governmental pricing programs could result in additional reimbursement requirements, penalties, sanctions and fines which could have a material adverse effect on our business, financial condition, results of operations and growth prospects.

We have certain price reporting obligations to the Medicaid Drug Rebate program, Medicare and/or other governmental pricing programs, such as state Medicaid supplemental rebate programs. We participate in the Medicaid Drug Rebate program and are, therefore, required to pay a rebate to each state Medicaid program for our covered outpatient drugs that are dispensed to Medicaid beneficiaries and paid for by a state Medicaid program as a condition of having federal funds being made available to the states for our drugs under Medicaid and Medicare Part B. Such rebates are based on pricing data reported by us on a monthly and quarterly basis to CMS, the federal agency that administers the Medicaid Drug Rebate program. These data include the AMP and best price, or BP, which, in general, represents the lowest price available from the manufacturer to any entity in the United States in any pricing structure, calculated to include all sales and associated rebates, discounts and other price concessions. Our failure to comply with any required price reporting and rebate payment obligations could negatively impact our financial results and could result in penalties.

The PPACA made significant changes to the Medicaid Drug Rebate program, such as expanding rebate liability from fee-for-service Medicaid utilization to include the utilization of Medicaid managed care organizations as well and changing the definition of AMP. The PPACA also increased the minimum Medicaid rebate, changed the calculation of the rebate for certain innovator products that qualify as line extensions of existing drugs; and capped the total rebate amount at 100% of AMP. Finally, the PPACA requires pharmaceutical manufacturers of branded prescription drugs to pay a branded prescription drug fee to the federal government. Congress could enact additional legislation that further increases Medicaid drug rebates or other costs and charges associated with participating in the Medicaid Drug Rebate program. CMS issued a final regulation, which became effective on April 1, 2016, to implement the changes to the Medicaid Drug Rebate program under the PPACA.

Federal law requires that any company that participates in the Medicaid Drug Rebate program also participate in the Public Health Service’s 340B program in order for federal funds to be available for the manufacturer’s drugs under Medicaid and Medicare Part B. The 340B program requires participating manufacturers to agree to charge statutorily

defined covered entities no more than the 340B "ceiling price" for the manufacturer's covered outpatient drugs. These 340B covered entities include a variety of community health clinics and other entities that receive health services grants from the Public Health Service, as well as hospitals that serve a disproportionate share of low-income patients. The PPACA expanded the list of covered entities to include certain free-standing cancer hospitals, critical access hospitals, rural referral centers and sole community hospitals, but exempts "orphan drugs" from the ceiling price requirements for these covered entities. The 340B ceiling price is calculated using a statutory formula based on AMP and the rebate amount for the covered outpatient drug as calculated under the Medicaid Drug Rebate program, and, in general, products subject to Medicaid price reporting and rebate liability are also subject to the 340B ceiling price calculation and discount requirement. Any additional future changes to the definition of AMP and the Medicaid rebate amount under the PPACA or otherwise could affect our 340B ceiling price calculations and negatively impact our results of operations.

The PPACA obligates the Secretary of the HHS to update the agreement that manufacturers must sign to participate in the 340b program to obligate a manufacturer to offer the 340B price to covered entities if the manufacturer makes the drug available to any other purchaser at any price and to report to the government the ceiling prices for its drugs. The Health

Table of Contents

Resources and Services Administration, or HRSA, has updated the agreement with participating manufacturers accordingly. The PPACA also obligates the Secretary of the HHS to create regulations and processes to improve the integrity of the 340B program. On January 5, 2017, HRSA issued a final regulation regarding the calculation of the 340B ceiling price and the imposition of civil monetary penalties on manufacturers that knowingly and intentionally overcharge covered entities. The effective date of the regulation has been delayed until July 1, 2019. Implementation of this final rule and the issuance of any other final regulations and guidance could affect our obligations under the 340B program in ways we cannot anticipate. In addition, legislation may be introduced that, if passed, would further expand the 340B program to additional covered entities or would require participating manufacturers to agree to provide 340B discounted pricing on drugs used in an inpatient setting.

Federal law also requires that a company that participates in the Medicaid Drug Rebate program report average sales price information each quarter to CMS for certain categories of drugs that are paid under the Medicare Part B program. Manufacturers calculate the average sales price based on a statutorily defined formula as well as regulations and interpretations of the statute by CMS. CMS uses these submissions to determine payment rates for drugs under Medicare Part B. Statutory or regulatory changes or CMS guidance could affect the average sales price calculations for LUXTURNA or our product candidates that achieve regulatory approval and the resulting Medicare payment rate and could negatively impact our results of operations.

Pricing and rebate calculations vary across products and programs, are complex, and are often subject to interpretation by us, governmental or regulatory agencies and the courts. In the case of our AMP and BP reported to the Medicaid Drug Rebate program, if we become aware that our reporting for a prior quarter was incorrect, or has changed as a result of recalculation of the pricing data, we are obligated to resubmit corrected data for up to three years after those data originally were due. Such restatements and recalculations would increase our costs for complying with the laws and regulations governing the Medicaid Drug Rebate program and could result in an overage or underage in our rebate liability for past quarters. Price recalculations also may affect the ceiling price at which we will be required to offer for LUXTURNA or our product candidates that achieve regulatory approval under the 340B program.

We will be liable for errors associated with our submission of pricing data. In addition to retroactive rebates and the potential for 340B program refunds, if we are found to have knowingly submitted any false price information to the government, we may be liable for significant civil monetary penalties per item of false information. If we are found to have made a misrepresentation in the reporting of our average sales price, the Medicare statute provides for significant civil monetary penalties for each misrepresentation for each day in which the misrepresentation was applied. Our failure to submit the required price data on a timely basis could result in a significant civil monetary penalty per day for each day the information is late beyond the due date. Such failure also could be grounds for CMS to terminate our Medicaid drug rebate agreement, pursuant to which we participate in the Medicaid Drug Rebate program. In the event that CMS terminates our Medicaid rebate agreement, federal payments may not be available under Medicaid or Medicare Part B for our covered outpatient drugs.

CMS and the HHS Office of Inspector General have pursued manufacturers that were alleged to have failed to report these data to the government in a timely manner. Governmental agencies may also make changes in program interpretations, requirements or conditions of participation, some of which may have implications for amounts previously estimated or paid. We cannot assure you that our submissions will not be found by CMS or other governmental agencies to be incomplete or incorrect.

In order to be eligible to have its products paid for with federal funds under the Medicaid and Medicare Part B programs and purchased by certain federal agencies and grantees, a manufacturer also must participate in the Department of Veterans Affairs Federal Supply Schedule, or FSS, pricing program, established by Section 603 of the Veterans Health Care Act of 1992, or the VHCA. Under this program, the manufacturer is obligated to make its innovator and single source products available for procurement on an FSS contract and charge a price to four federal agencies, Department of Veterans Affairs, or VA, Department of Defense, or DoD, Public Health Service, and Coast Guard, that is no higher than the statutory Federal Ceiling Price, or FCP. The FCP is based on the non federal average manufacturer price, or Non FAMP, which we calculate and report to the VA on a quarterly and annual basis. Pursuant to applicable law, knowing provision of false information in connection with a Non-FAMP filing can subject a manufacturer to significant civil penalties for each item of false information. These obligations also contain extensive

disclosure and certification requirements.

Moreover, pursuant to regulations issued by the DoD to implement Section 703 of the National Defense Authorization Act for Fiscal Year 2008, manufacturers are required to provide rebates on utilization of their innovator and single source products that are dispensed to TRICARE beneficiaries by TRICARE network retail pharmacies. The formula for determining the rebate is established in the regulations and is based on the difference between the annual Non-FAMP and the FCP (these price points are required to be calculated by us under the VHCA). The requirements under the FSS and TRICARE programs could reduce the revenue we may generate from any products that are commercialized in the future and could adversely affect our business and operating results.

Table of Contents

Product liability lawsuits against us could cause us to incur substantial liabilities and could limit commercialization of LUXTURNA and any other products that we may develop.

We face an inherent risk of product liability exposure related to the testing of our product candidates in clinical trials and may face an even greater risk as we commercialize LUXTURNA or any other products that we may develop. If we cannot successfully defend ourselves against claims that our product or product candidates caused injuries, we could incur substantial liabilities. Regardless of merit or eventual outcome, liability claims may result in:

- decreased demand for LUXTURNA and any other products that we may develop;
- loss of revenue;
- substantial monetary awards to trial participants or patients;
- significant time and costs to defend the related litigation;
- withdrawal or reduced enrollment of clinical trial participants;
- the inability to successfully commercialize LUXTURNA and any other products that we may develop; and
- injury to our reputation and significant negative media attention.

Although we maintain product liability insurance coverage, this insurance may not be adequate to cover all liabilities that we may incur. We anticipate that we will need to increase our insurance coverage each time we commence a clinical trial and/or commercialize an additional product. Insurance coverage is increasingly expensive. We may not be able to maintain insurance coverage at a reasonable cost or in an amount adequate to satisfy any liability that may arise.

If we fail to comply with environmental, health and safety laws and regulations, we could become subject to fines or penalties or incur costs that could have a material adverse effect on the success of our business.

We are subject to numerous environmental, health and safety laws and regulations, including those governing laboratory procedures and the generation, handling, use, storage, treatment, manufacture, transportation and disposal of, and exposure to, hazardous materials and wastes, as well as laws and regulations relating to occupational health and safety. Our operations involve the use of hazardous and flammable materials, including chemicals and biologic and radioactive materials. Our operations also produce hazardous waste products. We generally contract with third parties for the disposal of these materials and wastes. We cannot eliminate the risk of contamination or injury from these materials. In the event of contamination or injury resulting from our use of hazardous materials, we could be held liable for any resulting damages, and any liability could exceed our resources. We also could incur significant costs associated with civil or criminal fines and penalties.

Although we maintain workers' compensation insurance for certain costs and expenses we may incur due to injuries to our employees resulting from the use of hazardous materials or other work-related injuries, this insurance may not provide adequate coverage against potential liabilities. We do not maintain insurance for toxic tort claims that may be asserted against us in connection with our storage or disposal of biologic, hazardous or radioactive materials.

In addition, we may incur substantial costs in order to comply with current or future environmental, health and safety laws and regulations, which have tended to become more stringent over time. These current or future laws and regulations may impair our research, development or production efforts. Failure to comply with these laws and regulations also may result in substantial fines, penalties or other sanctions or liabilities, which could materially adversely affect our business, financial condition, results of operations and prospects.

Unfavorable global economic conditions could adversely affect our business, financial condition or results of operations.

Our results of operations could be adversely affected by general conditions in the global economy and in the global financial markets. The most recent global financial crisis caused extreme volatility and disruptions in the capital and credit markets. A severe or prolonged economic downturn, such as the most recent global financial crisis, could result in a variety of risks to our business, including weakened demand for our product and product candidates and our ability to raise additional capital when needed on acceptable terms, if at all. A weak or declining economy could strain our suppliers, possibly resulting in supply disruption, or cause delays in payments for our services by third-party payers or our collaborators. Any of the foregoing could harm our business and we cannot anticipate all of the ways in which the current economic climate and financial market conditions could adversely impact our business.

Third parties on which we rely and we may be adversely affected by natural disasters and our business continuity and disaster recovery plans may not adequately protect us from a serious disaster.

Table of Contents

Natural disasters could severely disrupt our operations and have a material adverse effect on our business, financial condition, results of operations and prospects. If a natural disaster, power outage or other event occurred that prevented us from using all or a significant portion of our headquarters, that damaged critical infrastructure or that otherwise disrupted operations, it may be difficult or, in certain cases, impossible for us to continue our business for a substantial period of time. The disaster recovery and business continuity plans we have in place currently are limited and may not prove adequate in the event of a serious disaster or similar event. Our manufacturing facility and substantially all of our current supply of product and product candidates are located in Philadelphia, Pennsylvania, and we do not have any existing back-up facilities in place or plans for such back-up facilities. We may incur substantial expenses as a result of the limited nature of our disaster recovery and business continuity plans, which could have a material adverse effect on our business, financial condition, results of operations and prospects.

Our internal computer systems, or those of our collaborators or other contractors or consultants, may fail or suffer security breaches, which could result in a material disruption of our product development programs.

Our internal computer systems and those of our current and any future collaborators and other contractors or consultants are vulnerable to damage from computer viruses, unauthorized access, natural disasters, terrorism, war and telecommunication and electrical failures. The size and complexity of our information technology systems, and those of our collaborators, contractors and consultants, and the large amounts of confidential information stored on those systems, make such systems vulnerable to service interruptions or to security breaches from inadvertent or intentional actions by our employees, third-party vendors and/or business partners, or from cyber-attacks by malicious third parties. Cyber-attacks are increasing in their frequency, sophistication and intensity, and have become increasingly difficult to detect. Cyber-attacks could include the deployment of harmful malware, ransomware, denial-of-service attacks, social engineering and other means to affect service reliability and threaten the confidentiality, integrity and availability of information. Cyber-attacks also could include phishing attempts or e-mail fraud to cause payments or information to be transmitted to an unintended recipient.

While we have not experienced a system failure, accident, cyber-attack or security breach that has resulted in a material interruption in our operations to date, if such an event were to occur, it could result in a material disruption of our development programs and our business operations, whether due to a loss of our trade secrets or other proprietary information or other similar disruptions. Additionally, any such event that leads to unauthorized access, use or disclosure of personal information, including personal information regarding our patients or employees, could harm our reputation, cause us not to comply with federal and/or state breach notification laws and foreign law equivalents and otherwise subject us to liability under laws and regulations that protect the privacy and security of personal information. Security breaches and other inappropriate access can be difficult to detect, and any delay in identifying them may lead to increased harm of the type described above. While we have implemented security measures to protect our information technology systems and infrastructure, there can be no assurance that such measures will prevent service interruptions or security breaches that could adversely affect our business and the further development and commercialization of our product and product candidates could be delayed.

Risks related to our intellectual property

Our rights to develop and commercialize LUXTURNA and our product candidates are subject, in part, to the terms and conditions of licenses granted to us by others.

We are heavily reliant upon licenses to certain patent rights and proprietary technology from third parties that are important or necessary to the development of our technology and products, including technology related to our manufacturing process and our gene therapy product and product candidates. These and other licenses may not provide exclusive rights to use such intellectual property and technology in all relevant fields of use and in all territories in which we may wish to develop or commercialize our technology and products in the future. As a result, we may not be able to prevent competitors from developing and commercializing competitive products in territories included in all of our licenses.

Licenses to additional third-party technology that may be required for our development programs may not be available in the future or may not be available on commercially reasonable terms, or at all, which could have a material adverse effect on our business, financial condition, results of operations and prospects.

In some circumstances, we may not have the right to control the preparation, filing and prosecution of patent applications, or to maintain the patents, covering technology that we license from third parties. For example, pursuant to each of our intellectual property licenses with CHOP, The Trustees of the University of Pennsylvania, Genethon, the NIH and the University of Iowa Research Foundation, our licensors retain control of such activities. Therefore, we cannot be certain that these patents and applications will be prosecuted, maintained and enforced in a manner consistent with the best interests of our business. If our licensors fail to maintain such patents, or lose rights to those patents or patent applications, the rights we have licensed may be reduced or eliminated and our right to develop and commercialize any of our products that are the subject of such licensed rights could be adversely affected. In addition to the foregoing, the risks associated with patent rights that we license from third parties will also apply to patent rights we may own in the future.

Table of Contents

Furthermore, the research resulting in certain of our licensed patent rights and technology was funded by the United States government. As a result, the government may have certain rights, or march-in rights, to such patent rights and technology. When new technologies are developed with government funding, the government generally obtains certain rights in any resulting patents, including a non-exclusive license authorizing the government to use the invention for non-commercial purposes. These rights may permit the government to disclose our confidential information to third parties and to exercise march-in rights to use or allow third parties to use our licensed technology. The government can exercise its march-in rights if it determines that action is necessary because we fail to achieve practical application of the government-funded technology, because action is necessary to alleviate health or safety needs, to meet requirements of federal regulations or to give preference to United States industry. In addition, our rights in such inventions may be subject to certain requirements to manufacture products embodying such inventions in the United States. Any exercise by the government of such rights could harm our competitive position, business, financial condition, results of operations and prospects.

If we are unable to obtain and maintain patent protection for our products and technology, or if the scope of the patent protection obtained is not sufficiently broad, our competitors could develop and commercialize products and technology similar or identical to ours, and our ability to successfully commercialize our products and technology may be adversely affected.

Our success depends, in large part, on our ability to obtain and maintain patent protection in the United States and other countries with respect to our proprietary product and product candidates and manufacturing technology. Our licensors have sought and we intend to seek to protect our proprietary position by filing patent applications in the United States and abroad related to many of our novel technologies and product and product candidates that are important to our business.

The patent prosecution process is expensive, time-consuming and complex, and we may not be able to file, prosecute, maintain, enforce or license all necessary or desirable patent applications at a reasonable cost or in a timely manner. In addition, certain patents in the field of gene therapy that may have otherwise potentially provided patent protection for certain of our product and product candidates have expired or will soon expire. In some cases, the work of certain academic researchers in the gene therapy field has entered the public domain, which we believe precludes our ability to obtain patent protection for certain inventions relating to such work. As a result, we have not sought, and may be unable to seek, patent protection for *SPK-CHM* to treat choroideremia. Consequently, we will not be able to assert any such patents to prevent others from using our technology for, and developing and marketing competing products to treat, these indications. It is also possible that we will fail to identify patentable aspects of our research and development output before it is too late to obtain patent protection.

We are a party to intellectual property license agreements with CHOP, Genethon, Penn and UIRF, each of which is important to our business, and we expect to enter into additional license agreements in the future. Our existing license agreements impose, and we expect that future license agreements will impose, various diligence, development and commercialization timelines, milestone payments, royalties and other obligations on us. If we fail to comply with our obligations under these agreements, or we are subject to a bankruptcy, the licensor may have the right to terminate the license, in which event we would not be able to market products covered by the license.

The patent position of biotechnology and pharmaceutical companies generally is highly uncertain, involves complex legal and factual questions and has, in recent years, been the subject of much litigation. As a result, the issuance, scope, validity, enforceability and commercial value of our patent rights are highly uncertain. Our pending and future patent applications may not result in patents being issued which protect our technology or product candidates or which effectively prevent others from commercializing competitive technologies and product candidates. Changes in either the patent laws or interpretation of the patent laws in the United States and other countries may diminish the value of our patents or narrow the scope of our patent protection.

We may not be aware of all third-party intellectual property rights potentially relating to our product candidates. Publications of discoveries in the scientific literature often lag the actual discoveries, and patent applications in the United States and other jurisdictions are typically not published until 18 months after filing or, in some cases, not at all. Therefore, we cannot be certain that we were the first to make the inventions claimed in any owned or any licensed patents or pending patent applications, or that we were the first to file for patent protection of such

inventions.

Even if the patent applications we license or may own in the future do issue as patents, they may not issue in a form that will provide us with any meaningful protection, prevent competitors or other third parties from competing with us or otherwise provide us with any competitive advantage. Our competitors or other third parties may be able to circumvent our patents by developing similar or alternative technologies or products in a non-infringing manner.

Table of Contents

The issuance of a patent is not conclusive as to its inventorship, scope, validity or enforceability, and our patents may be challenged in the courts or patent offices in the United States and abroad. Such challenges may result in loss of exclusivity or in patent claims being narrowed, invalidated or held unenforceable, which could limit our ability to stop others from using or commercializing similar or identical technology and products, or limit the duration of the patent protection of our technology and product and product candidates. Given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting such candidates might expire before or shortly after such candidates are commercialized. As a result, our intellectual property may not provide us with sufficient rights to exclude others from commercializing products similar or identical to ours.

Our intellectual property licenses with third parties may be subject to disagreements over contract interpretation, which could narrow the scope of our rights to the relevant intellectual property or technology or increase our financial or other obligations to our licensors.

The agreements under which we currently license intellectual property or technology from third parties are complex, and certain provisions in such agreements may be susceptible to multiple interpretations. The resolution of any contract interpretation disagreement that may arise could narrow what we believe to be the scope of our rights to the relevant intellectual property or technology, or increase what we believe to be our financial or other obligations under the relevant agreement, either of which could have a material adverse effect on our business, financial condition, results of operations and prospects.

If we fail to comply with our obligations in the agreements under which we license intellectual property rights from third parties or otherwise experience disruptions to our business relationships with our licensors, we could lose license rights that are important to our business.

We have entered into license agreements with third parties and may need to obtain additional licenses from others to advance our research or allow commercialization of our product candidates. It is possible that we may be unable to obtain additional licenses at a reasonable cost or on reasonable terms, if at all. In that event, we may be required to expend significant time and resources to redesign our product candidates or the methods for manufacturing them or to develop or license replacement technology, all of which may not be feasible on a technical or commercial basis. If we are unable to do so, we may be unable to develop or commercialize the affected product candidates, which could harm our business significantly. We cannot provide any assurances that third-party patents do not exist which might be enforced against our current manufacturing methods, product candidates or future methods or products, resulting in either an injunction prohibiting our manufacture or sales, or, with respect to our sales, an obligation on our part to pay royalties and/or other forms of compensation to third parties.

In each of our existing license agreements, and we expect in our future agreements, patent prosecution of our licensed technology is controlled solely by the licensor, and we are required to reimburse the licensor for their costs of patent prosecution. If our licensors fail to obtain and maintain patent or other protection for the proprietary intellectual property we license from them, we could lose our rights to the intellectual property or our exclusivity with respect to those rights, and our competitors could market competing products using the intellectual property. Further, in each of our license agreements we are responsible for bringing any actions against any third party for infringing on the patents we have licensed. Certain of our license agreements also require us to meet development thresholds to maintain the license, including establishing a set timeline for developing and commercializing products and minimum yearly diligence obligations in developing and commercializing the product. Disputes may arise regarding intellectual property subject to a licensing agreement, including:

- the scope of rights granted under the license agreement and other interpretation-related issues;
- the extent to which our technology and processes infringe on intellectual property of the licensor that is not subject to the licensing agreement;
- the sublicensing of patent and other rights under our collaborative development relationships;
- our diligence obligations under the license agreement and what activities satisfy those diligence obligations;
- the inventorship or ownership of inventions and know-how resulting from the joint creation or use of intellectual property by our licensors and us and our partners; and
- the priority of invention of patented technology.

If disputes over intellectual property that we have licensed prevent or impair our ability to maintain our current licensing arrangements on acceptable terms, we may be unable to successfully develop and commercialize the affected product candidates.

Table of Contents

We may not be successful in obtaining necessary rights to our product candidates through acquisitions and in-licenses.

We currently have rights to the intellectual property, through licenses from third parties, to develop our product candidates. Because our programs may require the use of proprietary rights held by third parties, the growth of our business likely will depend, in part, on our ability to acquire, in-license or use these proprietary rights. We may be unable to acquire or in-license any compositions, methods of use, processes or other intellectual property rights from third parties that we identify as necessary for our product candidates. The licensing or acquisition of third-party intellectual property rights is a competitive area, and several more established companies may pursue strategies to license or acquire third-party intellectual property rights that we may consider attractive. These established companies may have a competitive advantage over us due to their size, capital resources and greater clinical development and commercialization capabilities. In addition, companies that perceive us to be a competitor may be unwilling to assign or license rights to us. We also may be unable to license or acquire third-party intellectual property rights on terms that would allow us to make an appropriate return on our investment.

We sometimes collaborate with non-profit and academic institutions to accelerate our preclinical research or development under written agreements with these institutions. Typically, these institutions provide us with an option to negotiate a license to any of the institution's rights in technology resulting from the collaboration. Regardless of such option, we may be unable to negotiate a license within the specified timeframe or under terms that are acceptable to us. If we are unable to do so, the institution may offer the intellectual property rights to other parties, potentially blocking our ability to pursue our program.

If we are unable to successfully obtain rights to required third-party intellectual property rights or maintain the existing intellectual property rights we have, we may have to abandon development of the relevant program or product candidate and our business, financial condition, results of operations and prospects could suffer.

Obtaining and maintaining our patent protection depends on compliance with various procedural, document submission, fee payment and other requirements imposed by government patent agencies, and our patent protection could be reduced or eliminated for non-compliance with these requirements.

Periodic maintenance fees, renewal fees, annuity fees and various other government fees on patents and/or applications will be due to be paid to the USPTO, and various government patent agencies outside of the United States over the lifetime of our licensed patents and/or applications and any patent rights we may own in the future. We rely on our outside counsel or our licensing partners to pay these fees due to non-U.S. patent agencies. The USPTO and various non-U.S. government patent agencies require compliance with several procedural, documentary, fee payment and other similar provisions during the patent application process. We employ reputable law firms and other professionals to help us comply and we are also dependent on our licensors to take the necessary action to comply with these requirements with respect to our licensed intellectual property. In many cases, an inadvertent lapse can be cured by payment of a late fee or by other means in accordance with the applicable rules. There are situations, however, in which non-compliance can result in abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. In such an event, potential competitors might be able to enter the market and this circumstance could have a material adverse effect on our business.

We may not be able to protect our intellectual property rights throughout the world.

Filing, prosecuting and defending patents on product candidates in all countries throughout the world would be prohibitively expensive, and our intellectual property rights in some countries outside the United States could be less extensive than those in the United States. Although our license agreements with CHOP, Penn and UIRF grant us worldwide rights, certain of our in-licensed United States patent rights lack corresponding foreign patents or patent applications. For example, we license a United States patent from Penn that covers methods of treating patients with LCA due to *RPE65* mutations. No patents or patent applications outside the United States corresponding to this patent were ever pursued. In addition, the laws of some foreign countries do not protect intellectual property rights to the same extent as federal and state laws in the United States. Consequently, we may not be able to prevent third parties from practicing our inventions in all countries outside the United States, or from selling or importing products made using our inventions in and into the United States or other jurisdictions. Competitors may use our technologies in jurisdictions where we have not obtained patent protection to develop their own products and, further, may export

otherwise infringing products to territories where we have patent protection, but enforcement is not as strong as that in the United States. These products may compete with our products and our patents or other intellectual property rights may not be effective or sufficient to prevent them from competing.

Table of Contents

Many companies have encountered significant problems in protecting and defending intellectual property rights in foreign jurisdictions. The legal systems of certain countries, particularly certain developing countries, do not favor the enforcement of patents, trade secrets and other intellectual property protection, particularly those relating to biotechnology products, which could make it difficult for us to stop the infringement of our patents or marketing of competing products in violation of our proprietary rights generally. Proceedings to enforce our patent rights in foreign jurisdictions could result in substantial costs and divert our efforts and attention from other aspects of our business, could put our patents at risk of being invalidated or interpreted narrowly and our patent applications at risk of not issuing and could provoke third parties to assert claims against us. We may not prevail in any lawsuits that we initiate, and the damages or other remedies awarded, if any, may not be commercially meaningful. Accordingly, our efforts to enforce our intellectual property rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we develop or license.

Issued patents covering our product or product candidates could be found invalid or unenforceable if challenged in court. We may not be able to protect our trade secrets in court.

If one of our licensing partners or we initiate legal proceedings against a third party to enforce a patent covering our product or one of our product candidates, the defendant could counterclaim that the patent covering our product or product candidate is invalid or unenforceable. In patent litigation in the United States, defendant counterclaims alleging invalidity or unenforceability are commonplace. Grounds for a validity challenge could be an alleged failure to meet any of several statutory requirements, including lack of novelty, obviousness, written description or non-enablement. Grounds for an unenforceability assertion could be an allegation that someone connected with prosecution of the patent withheld information material to patentability from the USPTO, or made a misleading statement, during prosecution. Third parties also may raise similar claims before administrative bodies in the United States or abroad, even outside the context of litigation. Such mechanisms include re-examination, post grant review, *inter partes* review and equivalent proceedings in foreign jurisdictions. Such proceedings could result in the revocation or cancellation of or amendment to our patents in such a way that they no longer cover our product or product candidates. The outcome following legal assertions of invalidity and unenforceability is unpredictable. With respect to the validity question, for example, we cannot be certain that there is no invalidating prior art, of which the patent examiner and we or our licensing partners were unaware during prosecution. If a defendant were to prevail on a legal assertion of invalidity or unenforceability, we could lose at least part, and perhaps all, of the patent protection on one or more of our product or product candidates. Such a loss of patent protection could have a material adverse impact on our business.

In addition to the protection afforded by patents, we rely on trade secret protection and confidentiality agreements to protect proprietary know-how that is not patentable or that we elect not to patent, processes for which patents are difficult to enforce and any other elements of our product candidate discovery and development processes that involve proprietary know-how, information or technology that is not covered by patents. However, trade secrets can be difficult to protect and some courts inside and outside the United States are less willing or unwilling to protect trade secrets. We seek to protect our proprietary technology and processes, in part, by entering into confidentiality agreements with our employees, consultants, scientific advisors and contractors. We cannot guarantee that we have entered into such agreements with each party that may have or have had access to our trade secrets or proprietary technology and processes. We also seek to preserve the integrity and confidentiality of our data and trade secrets by maintaining physical security of our premises and physical and electronic security of our information technology systems. While we have confidence in these individuals, organizations and systems, agreements or security measures may be breached, and we may not have adequate remedies for any breach. In addition, our trade secrets may otherwise become known or be independently discovered by competitors.

Third parties may initiate legal proceedings alleging that we are infringing their intellectual property rights, the outcome of which would be uncertain and could have a material adverse effect on the success of our business.

Our commercial success depends upon our ability and the ability of our collaborators to develop, manufacture, market and sell LUXTURNA and our product candidates and use our proprietary technologies without infringing the proprietary rights and intellectual property of third parties. The biotechnology and pharmaceutical industries are characterized by extensive and complex litigation regarding patents and other intellectual property rights. We may in

the future become party to, or be threatened with, adversarial proceedings or litigation regarding intellectual property rights with respect to our product and product candidates and technology, including interference proceedings, post grant review and *inter partes* review before the USPTO. Third parties may assert infringement claims against us based on existing patents or patents that may be granted in the future, regardless of their merit. We are aware of certain third-party patents relating to gene delivery to ocular cells and certain vector manufacturing methods that may relate to, and potentially could be asserted to encompass, our LUXTURNA, *SPK-CHM, SPK-FIX, SPK-FVIII, SPK-GAA* and *SPK-TPP1* programs. There is a risk that third parties may choose to engage in litigation with us to enforce or to otherwise assert their patent rights against us. Even if we believe such claims are without merit, a court of competent jurisdiction could hold that these third-party patents are valid, enforceable and infringed, which could materially and adversely affect our ability to commercialize LUXTURNA and our product candidates in our *SPK-CHM*, *SPK-FVIII, SPK-GAA* and *SPK-TPP1* programs or any of our product candidates or technologies covered by the asserted third-party patents. In order to successfully challenge the validity of any such United States patent in federal court, we would need to

Table of Contents

overcome a presumption of validity. As this burden is a high one requiring us to present clear and convincing evidence as to the invalidity of any such United States patent claim, there is no assurance that a court of competent jurisdiction would invalidate the claims of any such United States patent. If we are found to infringe a third party's valid and enforceable intellectual property rights, we could be required to obtain a license from such third party to continue developing, manufacturing and marketing our product and product candidates and technology. However, we may not be able to obtain any required license on commercially reasonable terms or at all. Even if we were able to obtain a license, it could be non-exclusive, thereby giving our competitors and other third parties access to the same technologies licensed to us, and it could require us to make substantial licensing and royalty payments. We could be forced, including by court order, to cease developing, manufacturing and commercializing the infringing technology or product or product candidates. In addition, we could be found liable for monetary damages, including treble damages and attorneys' fees, if we are found to have willfully infringed a patent or other intellectual property right. A finding of infringement could prevent us from manufacturing and commercializing our product and product candidates or force us to cease some of our business operations, which could materially harm our business. Claims that we have misappropriated the confidential information or trade secrets of third parties could have a similar negative impact on our business, financial condition, results of operations and prospects.

Intellectual property litigation could cause us to spend substantial resources and distract our personnel from their normal responsibilities.

Competitors may infringe our patents or the patents of our licensing partners, or we may be required to defend against claims of infringement. To counter infringement or unauthorized use claims or to defend against claims of infringement can be expensive and time consuming. Even if resolved in our favor, litigation or other legal proceedings relating to intellectual property claims may cause us to incur significant expenses and could distract our technical and management personnel from their normal responsibilities. In addition, there could be public announcements of the results of hearings, motions or other interim proceedings or developments and if securities analysts or investors perceive these results to be negative, it could have a substantial adverse effect on the price of our common stock. Such litigation or proceedings could substantially increase our operating losses and reduce the resources available for development activities or any future sales, marketing or distribution activities. We may not have sufficient financial or other resources to adequately conduct such litigation or proceedings. Some of our competitors may be able to sustain the costs of such litigation or proceedings more effectively than we can because of their greater financial resources and more mature and developed intellectual property portfolios. Uncertainties resulting from the initiation and continuation of patent litigation or other proceedings could have a material adverse effect on our ability to compete in the marketplace.

We may be subject to claims asserting that our employees, consultants or advisors have wrongfully used or disclosed alleged trade secrets of their current or former employers or claims asserting ownership of what we regard as our own intellectual property.

Many of our employees, consultants or advisors are currently, or were previously, employed at universities or other biotechnology or pharmaceutical companies, including our competitors or potential competitors. Although we try to ensure that our employees, consultants and advisors do not use the proprietary information or know-how of others in their work for us, we may be subject to claims that these individuals or we have used or disclosed intellectual property, including trade secrets or other proprietary information, of any such individual's current or former employer. Litigation may be necessary to defend against these claims. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights or personnel. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to management.

In addition, while it is our policy to require our employees and contractors who may be involved in the conception or development of intellectual property to execute agreements assigning such intellectual property to us, we may be unsuccessful in executing such an agreement with each party who, in fact, conceives or develops intellectual property that we regard as our own. The assignment of intellectual property rights may not be self-executing or the assignment agreements may be breached, and we may be forced to bring claims against third parties, or defend claims that they may bring against us, to determine the ownership of what we regard as our intellectual property.

Changes in United States patent law could diminish the value of patents in general, thereby impairing our ability to protect our products.

Recent patent reform legislation could increase the uncertainties and costs surrounding the prosecution of patent applications and the enforcement or defense of issued patents. On September 16, 2011, the Leahy-Smith America Invents Act, or the Leahy-Smith Act, was signed into law. The Leahy-Smith Act includes several significant changes to United States patent law. These include provisions that affect the way patent applications are prosecuted and also may affect patent litigation. These also include provisions that switched the United States from a "first-to-invent" system to a "first-to-file" system, allow third-party submission of prior art to the USPTO during patent prosecution and set forth additional procedures to attack the validity of a patent by the USPTO administered post grant proceedings. Under a first-to-file system, assuming the other requirements

Table of Contents

for patentability are met, the first inventor to file a patent application generally will be entitled to the patent on an invention regardless of whether another inventor had made the invention earlier. The USPTO recently developed new regulations and procedures to govern administration of the Leahy-Smith Act, and many of the substantive changes to patent law associated with the Leahy-Smith Act, and in particular, the first to file provisions, only became effective on March 16, 2013. Accordingly, it is not clear what, if any, impact the Leahy-Smith Act will have on the operation of our business. However, the Leahy-Smith Act and its implementation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents, all of which could have a material adverse effect on our business, financial condition, results of operations and prospects.

The patent positions of companies engaged in the development and commercialization of biologics and pharmaceuticals are particularly uncertain. Two cases involving diagnostic method claims and "gene patents" have been decided by the Supreme Court of the United States, or Supreme Court. On March 20, 2012, the Supreme Court issued a decision in Mayo Collaborative Services v. Prometheus Laboratories, Inc., or Prometheus, a case involving patent claims directed to a process of measuring a metabolic product in a patient to optimize a drug dosage for the patient. According to the Supreme Court, the addition of well-understood, routine or conventional activity such as "administering" or "determining" steps was not enough to transform an otherwise patent-ineligible natural phenomenon into patent-eligible subject matter. On July 3, 2012, the USPTO issued a guidance memo to patent examiners indicating that process claims directed to a law of nature, a natural phenomenon or a naturally occurring relation or correlation that do not include additional elements or steps that integrate the natural principle into the claimed invention such that the natural principle is practically applied and the claim amounts to significantly more than the natural principle itself should be rejected as directed to not patent-eligible subject matter. On June 13, 2013, the Supreme Court issued its decision in Association for Molecular Pathology v. Myriad Genetics, Inc., or Myriad, a case involving patent claims held by Myriad Genetics, Inc. relating to the breast cancer susceptibility genes BRCA1 and BRCA2. Myriad held that an isolated segment of naturally occurring DNA, such as the DNA constituting the BRCA1 and BRCA2 genes, is not patent eligible subject matter, but that complementary DNA, which is an artificial construct that may be created from RNA transcripts of genes, may be patent eligible.

On March 4, 2014, the USPTO issued a guidance memorandum to patent examiners entitled "2014 Procedure For Subject Matter Eligibility Analysis Of Claims Reciting Or Involving Laws Of Nature/Natural Principles, Natural Phenomena, And/Or Natural Products." On December 6, 2014, a memorandum entitled "2014 Interim Guidance on Subject Matter Eligibility" was published. On July 30, 2015, an update pertaining to patent subject matter eligibility was published by the USPTO. Additional USPTO guidance memoranda concerning subject matter eligibility were issued on May 4, 2018, April 2, 2018, April 19, 2018, and June 7, 2018. These guidelines instruct USPTO examiners on the ramifications of the Prometheus and Myriad rulings and apply the Myriad ruling to natural products and principles including all naturally occurring nucleic acids. Patents for certain of our product candidates contain claims related to specific DNA sequences that are naturally occurring and, therefore, could be the subject of future challenges made by third parties. In addition, the recent USPTO guidance could make it impossible for us to pursue similar patent claims in patent applications we may prosecute in the future.

There can be no assurance that our efforts to seek patent protection for our technology and products will not be negatively impacted by the decisions described above, rulings in other cases or changes in guidance or procedures issued by the USPTO. We cannot fully predict what impact the Supreme Court's decisions in Prometheus and Myriad may have on the ability of life science companies to obtain or enforce patents relating to their products and technologies in the future. These decisions, the guidance issued by the USPTO and rulings in other cases or changes in USPTO guidance or procedures could have a material adverse effect on our existing patent portfolio and our ability to protect and enforce our intellectual property in the future.

Moreover, although the Supreme Court has held in Myriad that isolated segments of naturally occurring DNA are not patent-eligible subject matter, certain third parties could allege that activities that we may undertake infringe other gene-related patent claims, and we may deem it necessary to defend ourselves against these claims by asserting non-infringement and/or invalidity positions, or paying to obtain a license to these claims. In any of the foregoing or in other situations involving third-party intellectual property rights, if we are unsuccessful in defending against claims of patent infringement, we could be forced to pay damages or be subjected to an injunction that would prevent us from

utilizing the patented subject matter. Such outcomes could harm our business, financial condition, results of operations or prospects.

If we do not obtain patent term extension and data exclusivity for our product candidates, our business may be materially harmed.

Depending upon the timing, duration and specifics of any FDA marketing approval of our product candidates, one or more of our United States patents may be eligible for limited patent term extension under the Drug Price Competition and Patent Term Restoration Act of 1984, or Hatch-Waxman Amendments. The Hatch-Waxman Amendments permit a patent extension term of up to five years as compensation for patent term lost during FDA regulatory review process. A patent term extension cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval, only one patent may be extended and only those claims covering the approved drug, a method for using it or a method for manufacturing it may be extended. However, we may not be granted an extension because of, for example, failing to exercise due diligence during the

Table of Contents

testing phase or regulatory review process, failing to apply within applicable deadlines, failing to apply prior to expiration of relevant patents or otherwise failing to satisfy applicable requirements. Moreover, the applicable time period or the scope of patent protection afforded could be less than we request. We have filed an application seeking patent term extension on our LUXTURNA patent but there is a risk that the patent office will not approve the application. If we are unable to obtain patent term extension or the term of any such extension is less than we request, our competitors may obtain approval of competing products following our patent expiration, and our revenue could be reduced, possibly materially.

If our trademarks and trade names are not adequately protected, then we may not be able to build name recognition in our markets of interest and our business may be adversely affected.

We have registered trademarks with the USPTO for the mark "SPARK" and the Spark logo and pending trademark applications in the United States and various foreign jurisdictions for marks related to our business. Whether allowed or registered, our trademarks or trade names may be challenged, infringed, circumvented or declared generic or determined to be infringing on other marks. We may not be able to protect our rights to these trademarks and trade names, which we need to build name recognition among potential partners or customers in our markets of interest. At times, competitors may adopt trade names or trademarks similar to ours, thereby impeding our ability to build brand identity and possibly leading to market confusion. In addition, there could be potential trade name or trademark infringement claims brought by owners of other registered trademarks or trademarks that incorporate variations of our registered or unregistered trademarks or trade names. Over the long term, if we are unable to establish name recognition based on our trademarks and trade names, then we may not be able to compete effectively, and our business may be adversely affected. Our efforts to enforce or protect our proprietary rights related to trademarks, trade secrets, domain names, copyrights or other intellectual property may be ineffective and could result in substantial costs and diversion of resources and could adversely impact our business, financial condition, results of operations and prospects.

Intellectual property rights do not necessarily address all potential threats.

The degree of future protection afforded by our intellectual property rights is uncertain because intellectual property rights have limitations and may not adequately protect our business or permit us to maintain our competitive advantage. For example:

- others may be able to make gene therapy products that are similar to LUXTURNA or our product candidates but that are not covered by the claims of the patents that we license or may own in the future;
- we, or our license partners or current or future collaborators, might not have been the first to make the inventions covered by the issued patent or pending patent application that we license or may own in the future;
- we, or our license partners or current or future collaborators, might not have been the first to file patent applications covering certain of our or their inventions;
- others may independently develop similar or alternative technologies or duplicate any of our technologies without infringing our owned or licensed intellectual property rights;
- it is possible that our pending licensed patent applications or those that we may own in the future will not lead to issued patents;
- issued patents that we hold rights to may be held invalid or unenforceable, including as a result of legal challenges by our competitors;
- our competitors might conduct research and development activities in countries where we do not have patent rights and then use the information learned from such activities to develop competitive products for sale in our major commercial markets;
- we may not develop additional proprietary technologies that are patentable;
- the patents of others may have an adverse effect on our business; and
- we may choose not to file a patent for certain trade secrets or know-how, and a third party may subsequently file a patent covering such intellectual property.

Should any of these events occur, they could significantly harm our business, financial condition, results of operations and prospects.

Risks related to ownership of our common stock

The sale of a significant number of our total outstanding shares into the market could cause the market price of our common stock to drop significantly, even if our business is performing well.

Sales of a substantial number of shares of our common stock in the public market could occur at any time. These sales, or the perception in the market that holders of a large number of shares intend to sell shares, could reduce the market price of our

Table of Contents

common stock. Our outstanding shares of common stock may be freely sold in the public market at any time to the extent permitted by Rules 144 and 701 under the Securities Act of 1933, as amended, or the Securities Act, or to the extent such shares have already been registered under the Securities Act and are held by non-affiliates of ours. We have filed registration statements registering all shares of common stock that we may issue under our equity compensation plans. As of February 15, 2019, we had outstanding options to purchase an aggregate of 4,221,685 shares of our common stock, of which options to purchase 2,178,874 shares were vested. These shares can be freely sold in the public market upon issuance, subject to volume limitations and black-out periods applicable to affiliates. In addition, certain of our employees, executive officers, directors and affiliated stockholders have entered, or may enter into, Rule 10b5-1 plans providing for sales of shares of our common stock from time to time. Under a Rule 10b5-1 plan, a broker executes trades pursuant to parameters established by the employee, director or officer when entering into the plan, without further direction from the employee, officer, director or affiliated stockholder. A Rule 10b5-1 plan may be amended or terminated in some circumstances. Our employees, executive officers, directors and affiliated stockholders also may buy or sell additional shares outside of a Rule 10b5-1 plan when they are not in possession of material, nonpublic information.

If securities analysts do not publish research or reports about our business or if they publish negative evaluations of our stock, the price of our stock could decline.

The trading market for our common stock relies, in part, on the research and reports that industry or financial analysts publish about us or our business. Although we have obtained analyst coverage, if one or more of the analysts covering our business downgrade their evaluations of our stock, the price of our stock could decline. If one or more of these analysts cease to cover our stock or fail to regularly publish reports on us, we could lose visibility in the market for our stock, which in turn could cause our stock price to decline.

The price of our common stock may be volatile and fluctuate substantially, which could result in substantial losses for our stockholders.

Our stock price is likely to be volatile. The stock market in general, and the market for biopharmaceutical companies in particular, has experienced extreme volatility that has often been unrelated to the operating performance of particular companies. As a result of this volatility, our stockholders may not be able to sell their shares of common stock at or above the price they paid for their shares. The market price for our common stock may be influenced by many factors, including:

- the perceived likelihood of the completion of the proposed transaction with Roche;
- net sales of LUXTURNA;
- results of clinical trials of our product candidates or those of our competitors;
- the success of competitive products or technologies;
- commencement or termination of collaborations;
- regulatory or legal developments in the United States and other countries;
- developments or disputes concerning patent applications, issued patents or other proprietary rights;
- the recruitment or departure of key personnel;
- the level of expenses related to any of our product candidates or clinical development programs and the commercialization of LUXTURNA;
- the results of our efforts to discover, develop, acquire or in-license additional product candidates;
- actual or anticipated changes in estimates as to financial results, development timelines or recommendations by securities analysts;
- negative publicity around gene therapy in general, LUXTURNA or our product candidates;
- variations in our financial results or those of companies that are perceived to be similar to us;
- changes in the structure of healthcare payment systems;
- market conditions in the pharmaceutical and biotechnology sectors; and
- general economic, industry and market conditions.

If our quarterly operating results fall below the expectations of investors or securities analysts, the price of our common stock could decline substantially. Furthermore, any quarterly fluctuations in our operating results may, in turn, cause the price of our stock to fluctuate substantially. We believe that quarterly comparisons of our financial

results are not necessarily meaningful and should not be relied upon as an indication of our future performance.

Table of Contents

In the past, following periods of volatility in the market price of a company's securities, securities class-action litigation often has been instituted against that company. Such litigation, if instituted against us, could cause us to incur substantial costs to defend such claims and divert management's attention and resources, which could seriously harm our business, financial condition, results of operations and prospects.

We have broad discretion in the use of our cash, cash equivalents and marketable securities and may not use them effectively.

Subject to certain restrictions in our merger agreement with Roche, our management has broad discretion in the application of our cash, cash equivalents and marketable securities and could spend these funds in ways that do not improve our results of operations or enhance the value of our common stock. The failure by our management to apply these funds effectively could result in financial losses that could have a material adverse effect on our business, cause the price of our common stock to decline and delay the development and commercialization of our product and product candidates. Pending their use, we may invest our cash, cash equivalents and marketable securities in a manner that does not produce income or that loses value.

We incur substantial costs as a result of operating as a public company, and our management is now required to devote substantial time to new compliance initiatives.

As a public company, and particularly since December 31, 2016, when we ceased being an Emerging Growth Company, we incur significant legal, accounting and other expenses that we did not incur as a private company. In addition, the Sarbanes-Oxley Act of 2002 and rules subsequently implemented by the SEC and NASDAQ have imposed various requirements on public companies, including establishment and maintenance of effective disclosure and financial controls and corporate governance practices. Our management and other personnel devote a substantial amount of time to these compliance initiatives. Moreover, these rules and regulations have increased our legal and financial compliance costs and will make some activities more time-consuming and costly.

Pursuant to Section 404 of the Sarbanes-Oxley Act of 2002, or Section 404, we are required to furnish a report by our management on our internal control over financial reporting, including an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. To achieve compliance with Section 404 within the prescribed period, we will be engaged in a process to document and evaluate our internal control over financial reporting, which is both costly and challenging. In this regard, we will need to continue to dedicate internal resources, potentially engage outside consultants and adopt a detailed work plan to assess and document the adequacy of internal control over financial reporting, continue steps to improve control processes as appropriate, validate through testing that controls are functioning as documented and implement a continuous reporting and improvement process for internal control over financial reporting. Despite our efforts, there is a risk that neither we nor our independent registered public accounting firm will be able to conclude within the prescribed timeframe that our internal control over financial reporting is effective as required by Section 404. This could result in an adverse reaction in the financial markets due to a loss of confidence in the reliability of our financial statements.

Provisions in our corporate charter documents and under Delaware law could make an acquisition of us, which may be beneficial to our stockholders, more difficult and may prevent attempts by our stockholders to replace or remove our current management.

Provisions in our corporate charter and our bylaws may discourage, delay or prevent a merger, acquisition or other change in control of us that stockholders may consider favorable, including transactions in which stockholders might otherwise receive a premium for their shares. These provisions also could limit the price that investors might be willing to pay in the future for shares of our common stock, thereby depressing the market price of our common stock. In addition, because our board of directors is responsible for appointing the members of our management team, these provisions may frustrate or prevent any attempts by our stockholders to replace or remove our current management by making it more difficult for stockholders to replace members of our board of directors. Among other things, these provisions:

- establish a classified board of directors such that not all members of the board are elected at one time;
- allow the authorized number of our directors to be changed only by resolution of our board of directors;
- limit the manner in which stockholders can remove directors from the board;
-

establish advance notice requirements for stockholder proposals that can be acted on at stockholder meetings and nominations to our board of directors;

- require that stockholder actions must be effected at a duly called stockholder meeting and prohibit actions by our stockholders by written consent;
- limit who may call stockholder meetings;

Table of Contents

- authorize our board of directors to issue preferred stock without stockholder approval, which could be used to institute a shareholder rights plan, or so-called "poison pill," that would work to dilute the stock ownership of a potential hostile acquirer, effectively preventing acquisitions that have not been approved by our board of directors; and
- require the approval of the holders of at least 75% of the votes that all our stockholders would be entitled to cast to amend or repeal certain provisions of our charter or bylaws.

Moreover, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporation Law, which prohibits a person who owns in excess of 15% of our outstanding voting stock from merging or combining with us for a period of three years after the date of the transaction in which the person acquired in excess of 15% of our outstanding voting stock, unless the merger or combination is approved in a prescribed manner.

We recently amended our bylaws to designate the state courts in the State of Delaware as the sole and exclusive forum for certain types of actions and proceedings that may be initiated by our stockholders, which could discourage lawsuits against the Company and our directors, officers and employees.

On February 22, 2019 our board approved an amendment to our bylaws to provide that, unless we consent in writing to the selection of an alternative forum, the Court of Chancery of the State of Delaware will be the sole and exclusive forum for any derivative action or proceeding brought on our behalf, any action asserting a claim of breach of or based on a fiduciary duty owed by any of our current or former directors, officers or employees to the Company or our stockholders, any action asserting a claim against us or any of our current or former directors, officers or other employees or stockholder arising pursuant to any provision of the General Corporation Law of the State of Delaware or our certificate of incorporation or bylaws or as to which the General Corporation Law of the State of Delaware confers jurisdiction on the Court of Chancery of the State of Delaware, or any action asserting a claim against us governed by the internal affairs doctrine. This exclusive forum provision may limit the ability of our stockholders to bring a claim in a judicial forum that such stockholders find favorable for disputes with us or our directors, officers or employees, which may discourage such lawsuits against us and our directors, officers and employees.

Because we do not anticipate paying any cash dividends on our capital stock in the foreseeable future, capital appreciation, if any, will be stockholders' sole source of gain.

We have never declared or paid cash dividends on our capital stock. We currently intend to retain all of our future earnings, if any, to finance the growth and development of our business. In addition, the terms of any future debt agreements may preclude us from paying dividends. As a result, capital appreciation, if any, of our common stock will be stockholders' sole source of gain for the foreseeable future.

Item 1B. Unresolved Staff Comments.

None.

Item 2. Properties

We occupy approximately 28,000 square feet of office, laboratory and manufacturing space in Philadelphia, Pennsylvania, under a lease that expires in 2025, with our option for early termination in 2021. In February 2016, we entered into a lease for approximately 6,500 square feet of additional office space in Philadelphia for corporate and commercial purposes that expires in 2021.

In November 2016, we entered into an additional lease agreement for approximately 49,000 square feet of office space in Philadelphia, Pennsylvania, that commenced on April 1, 2017. In February 2017, we amended the lease to include approximately 25,000 additional square feet of office space that commenced on January 1, 2018. In November 2017, we amended this lease to accelerate the termination date of approximately 50,000 square feet of office space, with such termination to occur, at the latest, in December 2022.

In November 2017, we entered into a lease for approximately 108,000 square feet of office and laboratory space in Philadelphia, Pennsylvania through June 2033. In October 2018, we amended the lease to include approximately 55,000 additional square feet of office space.

Table of Contents

In May 2018, we entered in a lease agreement for approximately 14,000 square feet of office space in Philadelphia, Pennsylvania, that commenced on August 1, 2018 and expires in April 2020.

Item 3. Legal Proceedings

We are not currently subject to any material legal proceedings.

Item 4. Mine Safety Disclosures.
Not applicable.

Table of Contents

PART II.

Item 5. Market for Registrant's Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities

Our common stock is publicly traded on the Nasdaq Global Select Market under the symbol "ONCE".

Stock Performance Graph

The graph set forth below compares the cumulative total stockholder return on our common stock between January 30, 2015 (the first date that shares of our common stock were publicly traded) and December 31, 2018, with the cumulative total return of (a) the Nasdaq Biotechnology Index and (b) the Nasdaq Composite Index, over the same period. This graph assumes the investment of $100 after the market close on January 30, 2015 in each of our common stock, the Nasdaq Biotechnology Index and the Nasdaq Composite Index. The graph assumes our closing sale price on January 30, 2015 of $50.00 per share as the initial value of our common stock and not the initial offering price to the public in our initial public offering of $23.00 per share.

The comparisons shown in the graph below are based upon historical data. We caution that the stock price performance shown in the graph below is not necessarily indicative of, nor is it intended to forecast, the potential future performance of our common stock.

Comparison of Cumulative Returns: January 30, 2015 through December 31, 2018

Holders
As of February 15, 2019, there were approximately 29 holders of record of our common stock. This number does not include beneficial owners whose shares are held by nominees in street name.

Table of Contents

Dividends

We have not declared or paid any cash dividends on our common stock since our inception. We intend to retain future earnings, if any, to finance the operation and expansion of our business and do not anticipate paying any cash dividends in the foreseeable future.

Additionally, the Merger Agreement generally restricts, subject to certain limited exceptions (including, without limitation, Roche's prior written consent), our ability to pay any dividends on our common stock during the interim period between the execution of the Merger Agreement and the completion of the transaction (or the date on which the Merger Agreement is earlier terminated).

Information about our equity compensation plans

Information required by Item 5 of Form 10-K regarding our equity compensation plans is incorporated herein by reference to Item 12 of Part III of this Annual Report on Form 10-K.

Recent sales of unregistered securities

We did not sell any shares of our common stock or our preferred stock, or grant any stock options or restricted stock awards, during the year ended December 31, 2018 that were not registered under the Securities Act of 1933, as amended, or the Securities Act, and that have not otherwise been described in a Quarterly Report on Form 10-Q.

Purchase of equity securities

We did not purchase any of our registered equity securities during the period covered by this Annual Report on Form 10-K.

Table of Contents

Item 6. Selected Financial Data

The following selected financial data should be read together with our consolidated financial statements and the related notes appearing elsewhere in this Annual Report on Form 10-K and the "Management's Discussion and Analysis of Financial Condition and Results of Operations" section of this Annual Report on Form 10-K. The selected financial data below are derived from our consolidated financial statements. We have derived the statements of operations data for the years ended December 31, 2014 and 2015 and the balance sheet data as of December 31, 2014, 2015 and 2016 from our audited consolidated financial statements not included in this Annual Report on Form 10-K. We have derived the statements of operations data for the years ended December 31, 2016, 2017 and 2018 and the balance sheet data as of December 31, 2017 and 2018 from our audited consolidated financial statements included elsewhere in this Annual Report on Form 10-K. Our historical results are not necessarily indicative of the results to be expected in any future period.

	For the year ended December 31,				
	2014	2015	2016	2017	2018
	(in thousands, except share and per share data)				
Statement of operations data:					
Revenues:					
Product sales, net	$—	$—	$—	$—	$26,973
Contract revenues	634	22,064	20,183	12,066	37,752
Total revenues	634	22,064	20,183	12,066	64,725
Operating expenses:					
Cost of product sales	—	—	—	—	1,008
Cost of contract revenue	—	—	—	—	6,907
Research and development	16,351	46,030	86,380	135,160	125,254
Acquired in-process research and development	750	—	11,132	8,604	300
Impairment on in-process research and development	—	—	—	15,696	—
Selling, general and administrative	7,863	23,352	48,070	111,124	124,895
Total operating expenses	24,964	69,382	145,582	270,584	258,364
Loss from operations	(24,330)	(47,318)	(125,399)	(258,518)	(193,639)
Unrealized loss on equity investments	—	—	—	—	(5,078)
Interest income, net	5	192	1,746	4,073	9,994
Other income	—	—	—	—	110,000
Loss before income taxes	(24,325)	(47,126)	(123,653)	(254,445)	(78,723)
Income tax benefit (expense)	—	—	—	963	(99)
Net loss	(24,325)	(47,126)	(123,653)	(253,482)	(78,822)
Preferred stock dividends	(707)	(635)	—	—	—
Net loss applicable to common stockholders	$(25,032)	$(47,761)	$(123,653)	$(253,482)	$(78,822)
Basic and diluted net loss per common share (1)	$(4.64)	$(2.10)	$(4.29)	$(7.63)	$(2.11)
Weighted average basic and diluted common shares outstanding (1)	5,397,599	22,710,105	28,804,133	33,242,072	37,366,782

(1) See Note 3(n) to our audited consolidated financial statements for an explanation of the method used to calculate basic and diluted net loss per common share and weighted average basic and diluted common shares outstanding used to calculate the per common share amounts.

Table of Contents

	December 31,				
	2014	2015	2016	2017	2018
	(in thousands)				
Balance sheet data:					
Cash, cash equivalents and restricted cash	$74,567	$293,531	$58,923	$96,748	$148,247
Marketable securities	$—	$—	$259,143	$443,454	$453,037
Working capital	$61,509	$289,492	$284,596	$479,479	$504,786
Total assets	$90,446	$329,773	$373,863	$616,796	$814,352
Total stockholders' equity	$55,206	$290,538	$330,277	$513,624	$496,513

Table of Contents

Item 7. Management's Discussion and Analysis of Financial Condition and Results of Operations

The following discussion and analysis of our financial condition and results of operations should be read together with our consolidated financial statements and related notes appearing in this Annual Report on Form 10-K. Some of the information contained in this discussion and analysis or set forth elsewhere in this Annual Report on Form 10-K, including information with respect to our plans and strategy for our business, includes forward-looking statements that involve risks and uncertainties. As a result of many factors, including those factors set forth under Item 1A "Risk Factors" and under "Forward-looking statements" of this Annual Report on Form 10-K, our actual results could differ materially from the results described in, or implied by, the forward-looking statements contained in the following discussion and analysis. See "Forward-looking statements."

Overview

We are a leader in the field of gene therapy, seeking to transform the lives of patients suffering from debilitating genetic diseases by developing potentially one-time, life-altering treatments. The goal of gene therapy is to overcome the effects of a malfunctioning, disease-causing gene. Gene therapies have the potential to provide long-lasting effects, dramatically and positively changing the lives of patients with conditions where no, or only palliative, therapies exist. We have built a pipeline of gene therapy product candidates that are directed to the retina, the liver and the central nervous system.

In December 2017, the U.S. Food and Drug Administration, or FDA, approved LUXTURNA® (voretigene neparvovec-rzyl) for the treatment of patients with viable retinal cells and confirmed biallelic *RPE65* mutation-associated retinal dystrophy, a genetic blinding condition caused by mutations in the *RPE65* gene. LUXTURNA is the first FDA-approved gene therapy for a genetic disease, the first and only pharmacological treatment for an inherited retinal disease, or IRD, and the first adeno-associated virus, or AAV, vector gene therapy approved in the United States. LUXTURNA is manufactured at our manufacturing facility located in Philadelphia, which is the first licensed manufacturing facility in the United States for a gene therapy treating an inherited disease. LUXTURNA has received orphan drug status. In January 2018, we entered into a licensing and commercialization agreement with Novartis Pharma AG, or Novartis, for the development and commercialization of voretigene neparvovec outside the United States. In November 2018, we received approval from the European Medicines Agency, or EMA, for the marketing authorization of LUXTURNA in all 28-member states of the EU, as well as Iceland, Liechtenstein and Norway.

We are supporting the appropriate use of LUXTURNA in the United States through small, targeted commercial and medical affairs teams. LUXTURNA is administered by trained retinal surgeons at selected treatment centers in the United States that specialize in treating IRDs. In January 2018, we announced two novel payer programs to help ensure eligible patients in the United States have access to LUXTURNA: (i) an innovative contracting model that includes an option for direct-to-payer contracting; and (ii) an outcomes-based rebate arrangement with a short-term efficacy measure and a long-term durability measure.

We have three gene therapy product candidates, to which we retain global commercialization rights, in clinical development: (i) *SPK-8011*, our lead product candidate in the *SPK-FVIII* program for hemophilia A, (ii) *SPK-8016,* a product candidate for the hemophilia A inhibitor market, and (iii) *SPK-7001,* targeting choroideremia, or CHM. A fourth clinical-stage product candidate, *SPK-9001*, our lead product candidate in the *SPK-FIX* program for hemophilia B, recently was transitioned to Pfizer Inc., or Pfizer, pursuant to our license agreement. In July 2018, Pfizer announced the initiation of a Phase 3 program for *SPK-9001*, now referred to as PF-06838435 or fidanacogene elaparvovec.

In our *SPK-FVIII* program for the treatment of hemophilia A, we initiated a dose-escalating Phase 1/2 clinical trial for our lead product candidate, *SPK-8011*, in 2017. As of a November 2, 2018, data cutoff date, we had enrolled 12 participants in the trial: two at a dose of 5×10^{11} vector genomes (vg)/kilogram (kg) of body weight, three at a dose of 1×10^{12} vg/kg and seven at a dose of 2×10^{12} vg/kg. Across all 12 participants at the three doses tested, we saw a 94% reduction in bleeding and a 95% reduction in infusions. In the 2×10^{12} vg/kg dose cohort, five of the seven participants had reduced their overall bleeds and infusions by 100% and 99%, respectively (calculated based on data after week four). We also saw evidence of stable, durable factor VIII activity levels in all participants that have been followed for greater than one year. We demonstrated a dose response, with higher doses, on average, leading to higher

factor VIII levels. No participant developed factor VIII inhibitors, no thromboembolic events have been reported and transaminase elevations were infrequent and transient. One participant was electively admitted to the hospital to receive intravenous administration of methylprednisolone rather than having the infusions on an outpatient basis. The admission met the criteria for a serious adverse event, or SAE. We plan to incorporate a course of prophlactic steriods going forward in the development program.

We have scaled our mammalian cell-based suspension process to a 400 liter process and have achieved initial yields that are supportive of our future clinical and commercial requirements. Analytical and non-clinical testing demonstrated comparability of material manufactured with this suspension process to material manufactured with our adherent process. We have secured dedicated manufacturing capacity at Brammer Bio MA LLC's (Brammer Bio's) facility in Cambridge, Massachusetts.

Table of Contents

We recently initiated a Phase 3 clinical program for *SPK-8011*, beginning with a run-in study. In February 2018, FDA granted *SPK-8011* breakthrough therapy designation. We retain global commercialization rights to the *SPK-FVIII* program.

We have additional product candidates in the *SPK-FVIII* program that are intended to target specific sub-populations of hemophilia A patients, the first of which will target the hemophilia A inhibitor market using a novel, internally developed product candidate, *SPK-8016*. Our Investigational New Drug, or IND, for *SPK-8016* has been cleared and, per agreement with FDA, we initiated dosing in this Phase 1/2 study in a cohort similar to the patient cohort in our on-going *SPK-8011* Phase 1/2 study in order to establish safety before expanding into participants representing segments of the inhibitor market.

In December 2014, we entered into a global collaboration agreement with Pfizer for the development and commercialization of *SPK-FIX* product candidates for the treatment of hemophilia B. In July 2016, FDA granted breakthrough therapy designation to *SPK-9001,* the lead product candidate in our *SPK-FIX* program. In July 2018, we transitioned the program to Pfizer for Phase 3 development.

We are developing other liver-directed gene therapies, including *SPK-3006,* our lead product candidate for Pompe disease, an inherited lysosomal storage disorder caused by an enzyme deficiency that leads to accumulation of glycogen in cells, for which there are shortcomings in current enzyme replacement standard of care. In October 2018, we reported preclinical proof-of-concept data for *SPK-3006.*

SPK-7001 is our lead product candidate for the treatment of CHM, an IRD caused by mutations in the *REP-1* gene. We have completed enrollment of ten participants in two dose cohorts of our Phase 1/2 trial for *SPK-7001* and continue to follow subjects in the trial. In July 2017, we completed enrollment of five additional subjects in the trial who are at an earlier stage of disease. To date, *SPK-7001* has been well tolerated and we have not observed any product candidate-related SAEs in this trial. We have observed two SAEs that were deemed to be procedure related. We have received orphan product designation for *SPK-7001* for the treatment of CHM in both the United States and the European Union.

We have several product candidates in various stages of preclinical development. We have preclinical programs targeting IRDs, including Stargaardt's disease. We are developing neurodegenerative disease product candidates that are intended to address TPP1 deficiency, which is a form of Batten disease, and Huntington's disease, among others. We have received orphan product designation in the United States for *SPK-TPP1* for the treatment of CLN2 disease (neuronal ceroid lipofuscinosis (NCL)) caused by TPP1 deficiency.

We have incurred net losses since inception. We had an accumulated deficit of $589.7 million as of December 31, 2018. Substantially all of our net losses resulted from costs incurred in connection with our research and development programs and from selling, general and administrative expenses associated with our operations. For the years ended December 31, 2017 and 2018, we incurred $135.2 million and $125.3 million of research and development expenses, respectively, and $111.1 million and $124.9 million of selling, general and administrative expenses, respectively.

We expect to incur losses for the foreseeable future, and we expect these losses to increase as we continue our development of, and seek regulatory approvals for, our product candidates, hire additional personnel and commercialize any approved products, including LUXTURNA. Because of the numerous risks and uncertainties associated with product development and commercialization, we are unable to predict the timing or amount of increased expenses or when, or if, we will be able to achieve or maintain profitability. Even though we have generated revenues from the sale of commercial products, we may not become profitable. If we fail to become profitable, or are unable to sustain profitability on a continuing basis, then we may be unable to continue our operations at planned levels and be forced to reduce our operations.

Through December 31, 2018, we have received aggregate net proceeds from sales of our equity securities, after deducting underwriting discounts and commissions and other offering expenses payable by us, of $858.2 million.

In July 2018, we entered into a credit agreement with Wells Fargo Bank, National Association (Wells Fargo) as lender (the Credit Agreement), pursuant to which Wells Fargo extended a $50.0 million term loan to us, which bears interest at one-month LIBOR plus 0.65%, which rate is converted to a fixed rate per annum of 3.463% under a swap agreement. The term loan was fully drawn on the date of the Credit Agreement and matures on July 3, 2023. Through June 2019, we will only be obligated to make monthly interest payments with respect to the term loan. Thereafter, the

term loan will amortize in equal monthly installments through maturity. In connection with the Credit Agreement, we entered into a cash collateral and swap agreement with Wells Fargo on July 3, 2018.

On February 22, 2019, we entered into the Merger Agreement with Roche. Pursuant to the Merger Agreement, and upon the terms and subject to the conditions thereof, a wholly owned acquisition subsidiary of Roche will commence a cash tender offer, or the tender offer, to acquire all of the issued and outstanding shares of our common stock at a price per share of $114.50, net to the seller of such shares in cash, without interest, subject to any withholding of taxes required by applicable law. The completion of the tender offer will be conditioned on at least a majority of the shares of our outstanding common stock having been validly tendered into and not withdrawn from the offer, receipt of certain regulatory approvals, and other customary conditions. Following the completion of the tender offer, the acquisition subsidiary will merge with and into our

Table of Contents

company, with our company surviving as a wholly owned subsidiary of Roche. The merger will be governed by Section 251(h) of the General Corporation Law of the State of Delaware, with no stockholder vote required to consummate the merger. In the merger, each outstanding share of our common stock (other than shares of common stock held by us as treasury stock, or owned by Roche or Merger Sub or held by stockholders who are entitled to demand, and who properly demand, appraisal rights under Delaware law) will be converted into the right to receive $114.50 per share in cash, without interest, subject to any withholding of taxes required by applicable law. The transaction is expected to close in the second quarter of 2019.

Financial operations overview

Revenue

Product sales

LUXTURNA is distributed in the United States through two distribution models: (1) the traditional buy-and-bill model where the treatment center purchases and pays for the product and then submits a claim to the payer; and (2) our innovative contracting and distribution model, branded Spark PATH (Pioneering Access to Healthcare), that includes options for direct-to-payer contracting and outcomes-based rebates.

Our net product sales represent total gross product sales in the United States less allowances for estimated prompt-payment discounts, service fees, rebates and insurance co-payment assistance. Allowances are established based on contractual terms and management's reasonable estimates, as well as the expectation that 100% of the prompt-payment discounts will be earned. Product shipping and handling costs and distributor reporting fees are included in cost of product sales. We evaluated the variable consideration under Accounting Standards Codification (ASC) Topic 606, *Revenue from Contracts with Customers* (ASC 606), as it relates to the outcomes-based method and determined that based on historical clinical data, no additional reserves were required for the year ended December 31, 2018. All sales are recognized when control is transferred, which follows our verification of a scheduled LUXTURNA treatment.

Our product return policy is to provide non-monetary credit or product replacement. As the product is sold in direct relation to a scheduled treatment, we estimate that there is minimal risk of product return, including the risk of product expiration.

During the year ended December 31, 2018, we recognized $27.0 million in net product sales. Gross sales were $31.9 million, net of $4.9 million of product sales allowances. We expect that net product sales of LUXTURNA will fluctuate quarter over quarter, in particular as we continue to build and promote access. Net product sales for the year ended December 31, 2018, may not be representative of our sales for any future period.

Contract revenue

In December 2014, we entered into a global collaboration agreement with Pfizer for the development and commercialization of product candidates in our *SPK-FIX* program for the treatment of hemophilia B. Under this collaboration, we maintained responsibility for the clinical development of *SPK-FIX* product candidates through the completion of Phase 1/2 trials, which completion occurred in July 2018. Thereafter, Pfizer has responsibility for further clinical development, regulatory approvals and commercialization. In connection with entering into this agreement, we received a $20.0 million upfront payment. In November 2017, we amended our global collaboration agreement with Pfizer. Under the terms of this amendment, we received $15.0 million in payments upfront, and an additional $10.0 million upon completion of certain transition activities. In February 2018, we entered into a supply agreement with Pfizer to begin production in 2018 for one batch of drug substance expected to be used for Phase 3 development. We received $7.0 million upfront and received $7.0 million upon delivery. In July 2018, Pfizer announced the initiation of a Phase 3 program following our transfer of responsibility for the hemophilia B gene therapy program to Pfizer.

In January 2018, we entered into a licensing and commercialization agreement with Novartis (Novartis License Agreement) to develop and commercialize voretigene neparvovec (also known as LUXTURNA) outside the United States. Under the terms of the Novartis License Agreement, we have granted Novartis an exclusive right and license, with the right to grant certain sublicenses, under our intellectual property reasonably necessary or useful for the development or commercialization of LUXTURNA for the treatment, prevention, cure or control of *RPE65*-mediated IRD in humans outside the United States. Under the terms of the Novartis License Agreement, we received a

non-refundable, one-time payment of $105.0 million in the first quarter of 2018, and were eligible to receive up to an additional $65.0 million in milestone payments. We also are entitled to receive royalty payments at a percentage of net sales on a royalty-region by royalty-region basis, subject to reduction and extension in certain circumstances.
In conjunction with the Novartis License Agreement, we and Novartis also entered into a Supply Agreement, under which we have agreed to supply all of the commercial supply of voretigene neparvovec required by Novartis, subject to certain conditions.

Table of Contents

During the fourth quarter of 2018, and in conjunction with the European Commission granting marketing authorization for LUXTURNA, we earned an additional $25.0 million milestone payment and recorded an additional $30.0 million of variable consideration that was no longer constrained which, along with the $105.0 million upfront payment, is included as deferred revenue on our consolidated balance sheet as of December 31, 2018.

During the years ended December 31, 2016, 2017 and 2018, we recognized $20.2 million, $12.1 million and $37.8 million of contract revenue, respectively, related to our Pfizer and Novartis agreements.

Research and development expenses

Research and development expenses consist primarily of internal and external costs incurred for the development of our product candidates, which include:

- employee-related expenses, including salaries, benefits, travel and other compensation expenses, including stock-based compensation;
- expenses incurred under our agreements with contract research organizations, or CROs, and clinical sites that will conduct our preclinical studies and clinical trials and the cost of clinical consultants;
- costs associated with regulatory filings;
- costs of laboratory supplies and the acquiring, developing and manufacturing of preclinical and clinical study materials; and
- costs of facilities, depreciation and other expenses, which include direct and allocated expenses for rent and maintenance of facilities, insurance and other operating costs for the portion of our facilities related to research and development.

Research and development costs are expensed as incurred. Expenses for certain development activities are recognized based on an evaluation of the progress to completion of specific tasks using information and data provided by our vendors and our clinical sites.

We plan to increase our research and development expenses for the foreseeable future as we continue development of our product candidates. Our current and planned research and development activities include the following:

- expanding our medical affairs group;
- the Phase 1/2 clinical trials for *SPK-7001, SPK-8011, SPK-8016* and *SPK-3006*;
- the Phase 3 clinical trial for *SPK-8011*;
- research and development for our preclinical programs; and
- continued acquisition and manufacture of clinical trial materials in support of our clinical trials.

The successful development of our product candidates is highly uncertain and subject to numerous risks including, but not limited to:

- the scope, rate of progress and expense of our research and development activities;
- clinical trial results;
- the scope, terms and timing of regulatory approvals;
- the expense of filing, prosecuting, defending and enforcing patent claims and other intellectual property rights;
- the cost, timing and our ability to manufacture sufficient clinical and commercial supplies for any product candidates and products that we may develop; and
- the risks disclosed in the section entitled “Risk Factors” in this Annual Report on Form 10-K.

A change in the outcome of any of these variables could mean a significant change in the expenses and timing associated with the development of any product candidate.

Selling, general and administrative expenses

Selling, general and administrative expenses consist primarily of salaries and related costs, including stock-based compensation and travel expenses, for our employees in operational, finance, legal, business development, commercial and

Table of Contents

human resource functions. Other selling, general and administrative expenses include facility-related costs, professional fees for directors, accounting and legal services, consultants and expenses associated with obtaining and maintaining patents.

We anticipate that our selling, general and administrative expenses will increase in the future as we increase our headcount to support our continued growth and the commercialization of our approved products. We also anticipate increases in expenses related to audit, legal, regulatory and tax-related services associated with maintaining compliance as a public company, director and officer insurance premiums and investor relations costs. With the approval of our first product, LUXTURNA, in December 2017, we have incurred, and anticipate incurring further, increases in payroll and related expenses as a result of our commercial operations, especially as they relate to sales and marketing.

Critical accounting policies and significant judgments and estimates

Management's discussion and analysis of our financial condition and results of operations is based on our consolidated financial statements, which have been prepared in accordance with U.S. generally accepted accounting principles. The preparation of these consolidated financial statements requires us to make estimates and judgments that affect the reporting amounts of assets, liabilities, revenues and expenses and the disclosure of contingent assets and liabilities in our consolidated financial statements. On an ongoing basis, we evaluate our estimates and judgments, including those related to accrued expenses and stock-based compensation. We base our estimates on historical experience, known trends and events and various other factors that we believe to be reasonable under the circumstances, the results of which form the basis for making judgments about the carrying value of assets and liabilities that are not readily apparent from other sources. Actual results may differ from these estimates under different assumptions or conditions.

While our significant accounting policies are described in more detail in the notes to our consolidated financial statements appearing elsewhere in this Annual Report on Form 10-K, we believe the following accounting policies to be the most critical to the judgments and estimates used in the preparation of our consolidated financial statements.

Revenue recognition

Prior to 2018, we generated revenue solely through license and collaboration arrangements. In the first quarter of 2018, we adopted ASC 606. The adoption of this guidance resulted in no cumulative adjustment to our consolidated financial statements.

ASC 606 applies to all contracts with customers, except for contracts that are within the scope of other standards, such as leases, insurance, collaboration arrangements and financial instruments. Under ASC 606, an entity recognizes revenue when its customer obtains control of promised goods or services in an amount that reflects the consideration the entity expects to receive in exchange for those goods or services. To determine revenue recognition for arrangements that an entity determines are within the scope of ASC 606, the entity performs the following five steps: (i) identify the contract(s) with a customer; (ii) identify the performance obligations in the contract; (iii) determine the transaction price; (iv) allocate the transaction price to the performance obligations in the contract; and (v) recognize revenue when (or as) the entity satisfies a performance obligation. At contract inception, once the contract is determined to be within the scope of ASC 606, we assess the goods or services promised within each contract and determine those that are performance obligations and assess whether each promised good or service is distinct. We then recognize as revenue the amount of the transaction price that is allocated to the respective performance obligation when (or as) the performance obligation is satisfied.

Product sales

LUXTURNA is distributed in the United States through two distribution models: (1) the traditional buy-and-bill model where the treatment center purchases and pays for the product and then submits a claim to the payer; and (2) our innovative contracting and distribution model, branded Spark PATH, which includes options for direct-to-payer contracting and outcomes-based rebates.

Our net product sales represent total gross product sales in the United States less allowances for estimated discounts, service fees, rebates and insurance co-payment assistance. Allowances are established based on contractual terms and management's reasonable estimates, as well as the expectation that 100% of the prompt-payment discounts will be earned. Product shipping and handling costs and distributor reporting fees are included in cost of product sales. All

sales are recognized when control is transferred, which follows our verification of a scheduled LUXTURNA treatment.

Our product return policy is to provide non-monetary credit or product replacement. As the product is sold in direct relation to a scheduled treatment, we estimate that there is minimal risk of product return, including the risk of product expiration.

Research and development costs and expenses

Research and development costs are expensed as incurred. We recognize costs for certain development activities based on an evaluation of the progress to completion of specific tasks using information and data provided to us by our vendors and our

Table of Contents

clinical sites. We determine accrual estimates based on estimates of the services received and efforts expended that take into account discussion with applicable personnel and service providers as to the progress or state of completion of trials. Our clinical trial accrued and prepaid assets are dependent, in part, upon the receipt of timely and accurate reporting from CROs and other third-party vendors. Although we do not expect our estimates to differ materially from amounts we actually incur, our understanding of the status and timing of services or relative to the actual status and timing of services performed may vary and may result in us reporting amounts that are too high or too low for any particular period. When contracts for outside research or testing require advance payment, they are recorded on the consolidated balance sheet as prepaid items and expensed when the service is provided or reaches a specific milestone outlined in the contract.

Results of operations

Comparison of the years ended December 31, 2016 and 2017

	Year ended December 31,	
	2016	2017
	(in thousands)	
Contract revenues	$20,183	$12,066
Operating expenses:		
Research and development	86,380	135,160
Acquired in-process research and development	11,132	8,604
Impairment of acquired in-process research and development	—	15,696
Selling, general and administrative	48,070	111,124
Total operating expenses	145,582	270,584
Loss from operations	(125,399)	(258,518)
Interest income, net	1,746	4,073
Loss before income taxes	(123,653)	(254,445)
Income tax benefit	—	963
Net loss	$(123,653)	$(253,482)

Contract revenue

In the year ended December 31, 2016, we recognized $20.2 million of contract revenue, all of which was associated with our Pfizer agreement, including a $15.0 million milestone payment. In the year ended December 31, 2017, we recognized $12.1 million in contract revenue, all of which was associated with our Pfizer agreement.

Research and development expenses

Our research and development expenses for the year ended December 31, 2016 were $86.4 million and for the year ended December 31, 2017 were $135.2 million. The $48.8 million increase was due to a $40.4 million increase in internal research and development expenses, due to increased effort and headcount in research, technical operations and manufacturing, diagnostics, quality assurance and quality control and an increase of $8.4 million in external research and development expenses. The increase in external research and development was primarily from an increase of $4.4 million in expenses related to our *SPK-FVIII* program, $1.9 million in our *SPK-CHM* and *SPK-FIX* programs, $1.5 million related to our other programs in preclinical development and a $0.6 million increase in expenses related to LUXTURNA.

Table of Contents

The following table summarizes our research and development expenses by product candidate or program for the years ended December 31, 2016 and 2017:

	Year ended December 31,	
	2016	2017
	(in thousands)	
External research and development expenses:		
LUXTURNA	$10,703	$11,258
SPK-CHM	1,328	2,240
SPK-FIX	1,692	2,731
SPK-FVIII	3,268	7,694
Programs in preclinical development	7,316	8,784
Total external research and development expenses	24,307	32,707
Total internal research and development expenses	62,073	102,453
Total research and development expenses	$86,380	$135,160

We do not allocate personnel-related costs, including stock-based compensation, costs associated with broad technology platform improvements or other indirect costs, to specific programs, as they are deployed across multiple projects under development and, as such, are separately classified as internal research and development expenses in the table above.

Acquired in-process research and development expense

We recognize acquired in-process research and development, or IPR&D, expense for licensed technologies because of the additional research and development efforts and marketing approval required for commercialization. Our acquired IPR&D expense for the year ended December 31, 2016 was $11.1 million. Our acquired IPR&D expense for the year ended December 31, 2017 was $8.6 million. This amount includes $6.9 million of expense related to payments made in connection with a license agreement entered into with Selecta that provides us with exclusive worldwide rights to Selecta's proprietary SVP platform technology for co-administration with gene therapy targets.

Impairment of acquired in-process research and development expense

During the year ended December 31, 2017, it was determined that we would no longer pursue product candidates utilizing the technology acquired from Genable in March 2016 and, accordingly, we recorded a non-cash impairment charge of $15.7 million. Additionally, we recognized an income tax benefit of $1.0 million related to the reversal of the deferred tax liability associated with the acquired IPR&D during the year ended December 31, 2017.

Selling, general and administrative expenses

Our selling, general and administrative expenses for the year ended December 31, 2016 were $48.1 million and for the year ended December 31, 2017 were $111.1 million. Selling, general and administrative expenses consisted primarily of salaries and related costs, including stock-based compensation, legal and patent costs, professional fees and other operating costs. The $63.0 million increase primarily was due to an increase of $27.8 million in salaries and related costs, including stock-based compensation, due to increased headcount, an increase of $11.9 million in launch preparation activities for LUXTURNA and $14.7 million in legal and patent expenses, professional fees and other operating costs. It also includes an increase in facility-related costs of $8.6 million, primarily driven by $6.9 million of expense related to an early termination of one of our leases that was amended in November 2017.

88

Table of Contents

Comparison of the years ended December 31, 2017 and 2018

	Year ended December 31,	
	2017	2018
	(in thousands)	
Revenues:		
Product sales, net	$—	$26,973
Contract revenue	12,066	37,752
Total revenues	12,066	64,725
Operating expenses:		
Cost of product sales	—	1,008
Cost of contract revenue	—	6,907
Research and development	135,160	125,254
Acquired in-process research and development	8,604	300
Impairment of acquired in-process research and development	15,696	—
Selling, general and administrative	111,124	124,895
Total operating expenses	270,584	258,364
Loss from operations	(258,518)	(193,639)
Unrealized loss on equity investments	—	(5,078)
Interest income, net	4,073	9,994
Other income	—	110,000
Loss before income taxes	(254,445)	(78,723)
Income tax benefit (expense)	963	(99)
Net loss	$(253,482)	$(78,822)

Revenues

In the year ended December 31, 2018, we recognized $64.7 million in total revenues, of which $27.0 million was net product sales of LUXTURNA and $37.8 million was associated with our agreements with Pfizer and Novartis. In the year ended December 31, 2017, we recognized $12.1 million in total contract revenue associated with our Pfizer agreement.

Cost of product sales

Cost of product sales in the year ended December 31, 2018 was $1.0 million, and consists of manufacturing, shipping and other costs, as well as royalties. A substantial portion of the inventory sold during the year was produced prior to FDA approval and, therefore, was expensed previously as research and development.

Cost of contract revenue

Cost of contract revenue in the year ended December 31, 2018 was $6.9 million, and consists of manufacturing and other costs associated with our contract agreements.

Research and development expenses

Our research and development expenses for the year ended December 31, 2018 were $125.3 million compared with $135.2 million for the year ended December 31, 2017. The $9.9 million decrease was due to a $13.3 million reduction in internal research and development expenses, partially offset by an increase of $3.4 million in external research and development expenses. The $13.3 million reduction in internal research and development expense primarily was the result of $20.5 million in salaries and other LUXTURNA costs being capitalized as inventory following FDA approval, as well as costs associated with contract revenue. These costs were partially offset by an increase of $7.5 million in salaries and other related benefits. The $3.4 million growth in external research and development expenses primarily resulted from $14.4 million in increased expenses related to our hemophilia A program and $0.7 million in programs in preclinical development. These costs were partially offset by $7.9 million less in expenses related to LUXTURNA and $3.8 million less in expenses related to the *SPK-FIX* and *SPK-CHM* clinical programs.

89

Table of Contents

The following table summarizes our research and development expenses by product candidate or program for the years ended December 31, 2017 and 2018:

	Year ended December 31,	
	2017	2018
	(in thousands)	
External research and development expenses:		
LUXTURNA	$11,258	$3,395
SPK-CHM	2,240	844
SPK-FIX	2,731	318
SPK-FVIII	7,694	22,060
Programs in preclinical development	8,784	9,473
Total external research and development expenses	32,707	36,090
Total internal research and development expenses	102,453	89,164
Total research and development expenses	$135,160	$125,254

We do not allocate personnel-related costs, including stock-based compensation, costs associated with broad technology platform improvements or other indirect costs, to specific programs, as they are deployed across multiple projects under development and, as such, are separately classified as internal research and development expenses in the table above.

Acquired in-process research and development expense

Our acquired IPR&D expense for the year ended December 31, 2017, was $8.6 million. This amount includes $6.9 million of expense related to payments made in connection with a license agreement entered into with Selecta that provides us with exclusive worldwide rights to Selecta's proprietary SVP platform technology for co-administration with gene therapy targets.

Impairment of acquired in-process research and development expense

During the year ended December 31, 2017, it was determined that we would no longer pursue product candidates utilizing the technology acquired from Genable in March 2016 and, accordingly, we recorded a non-cash impairment charge of $15.7 million. Additionally, we recognized an income tax benefit of $1.0 million related to the reversal of the deferred tax liability associated with the acquired IPR&D during the year ended December 31, 2017.

Selling, general and administrative expenses

Selling, general and administrative expenses for the year ended December 31, 2018, were $124.9 million compared with $111.1 million for the year ended December 31, 2017. Selling, general and administrative expenses consist primarily of salaries and related costs, including stock-based compensation, legal and patent costs, facility costs and other professional fees. The $13.8 million growth primarily was due to an increase of $14.9 million in salaries and related costs, including stock-based compensation, and a $6.1 million increase in legal and patent expenses, professional fees and other operating costs. These increases were partially offset by a reduction of $6.9 million related to an early termination of one of our leases that was amended in 2017 and $0.3 million in launch activities for LUXTURNA.

Other income

We recognized $110.0 million of other income during the year ended December 31, 2018, from the sale of our rare pediatric disease priority review voucher, or PRV.

90

Table of Contents

Liquidity and capital resources

The following table sets forth the primary sources and uses of cash and cash equivalents for each year set forth below:

	Year ended December 31,		
	2016	2017	2018
	(in thousands)		
Net cash provided by (used in):			
Operating activities	$(80,442)	$(154,536)	$(70,563)
Investing activities	(285,520)	(207,732)	59,163
Financing activities	131,366	400,274	62,951
Effect of exchange rate changes on cash and cash equivalents and restricted cash	(12)	(181)	(52)
Net (decrease) increase in cash and cash equivalents and restricted cash	$(234,608)	$37,825	$51,499

Net cash used in operating activities

Net cash used in operating activities was $70.6 million for the year ended December 31, 2018, and consisted of a net loss of $78.8 million adjusted for non-cash items, including depreciation and amortization expense of $6.9 million, stock-based compensation expense of $48.6 million, non-cash rent income of $2.5 million, a loss on disposal of equipment of $0.1 million, an unrealized loss on equity investments of $5.1 million, non-cash interest income of $1.1 million and acquired in-process research and development expense of $0.3 million related to a license agreement. Net cash used in operating activities also included a net change in operating assets and liabilities of $60.9 million. The significant items in the change in operating assets include an increase in trade and other receivables of $39.5 million, primarily due to Pfizer receivables related to our global collaboration and supply agreements and trade receivables related to LUXTURNA sales. The change in operating assets also includes an increase of $35.3 million in prepaid expenses and other assets primarily related to Novartis milestone payments and an increase of $25.6 million of inventory as a result of the commercialization of LUXTURNA. The significant items in the change in operating liabilities include an increase in accounts payable and accrued expenses of $8.7 million mainly due to an increase in accruals related to bonus and other related salary accruals as a result of increased headcount. The change in operating liabilities also includes an increase in deferred revenue of $148.0 million primarily due to our Novartis agreement offset by revenue recognized related to our Pfizer agreement, an increase of $4.0 million in deferred rent related to tenant improvement allowances and an increase in other liabilities of $0.6 million.

Net cash used in operating activities was $154.5 million for the year ended December 31, 2017, and consisted of a net loss of $253.5 million adjusted for non-cash items and other adjustments, including a $15.7 million impairment charge on our acquired in-process research and development associated with our Genable acquisition in March 2016 and a non-cash income tax benefit for the reversal of the deferred tax liability associated with the impairment of $1.0 million. Other adjustments include an $8.6 million charge for acquired in-process research and development, which included additional payments and equity investments related to our collaboration agreement with Selecta, depreciation and amortization expense of $4.9 million, stock-based compensation expense of $41.4 million and non-cash rent expense of $0.5 million. Net cash used in operating activities also included a net change in operating assets and liabilities of $30.1 million. The significant items in the change in operating assets include a decrease in other receivables of $8.9 million, primarily driven by a $15.0 million payment received on our Pfizer receivable, and an increase of $3.2 million in prepaid expenses and other assets as a result of prepayments related to preclinical and clinical expenses. The significant items in the change in operating liabilities include an increase in accounts payable and accrued expenses of $13.0 million, mainly due to an increase in accruals related to bonus and other related salary accruals as a result of increased headcount. The change in operating liabilities also includes an increase in deferred rent of $1.6 million related to tenant improvement allowances, an increase in deferred revenue of $2.9 million due to an amendment to our Pfizer agreement executed in November 2017, and an increase in other liabilities of $6.8 million due to a lease termination liability related to the November 2017 amendment to one of our leases.

The net cash used in operating activities was $80.4 million for the year ended December 31, 2016, and consisted of a net loss of $123.7 million adjusted for non-cash items, including depreciation and amortization expense of $3.6 million, acquired in-process research and development of $11.1 million, stock-based compensation expense of $24.5 million, non-cash rent income of $0.5 million and a net change in operating assets and liabilities of $4.3 million. The

significant items in the change in operating assets and liabilities include a decrease in deferred revenue of $5.2 million, all of which is related to our Pfizer agreement, and an increase of $10.0 million in accounts payable and accrued expenses mainly due to an increase in accruals

Table of Contents

related to bonus and other related salary accruals as a result of increased headcount. and an increase of $0.5 million in prepaid expenses and other assets and other receivables.

Net cash provided by (used in) investing activities

Net cash provided by investing activities for the year ended December 31, 2018, was $59.2 million which included $110.0 million in proceeds from the sale of our PRV, offset by costs related to the net purchases of marketable securities of $14.7 million, the purchase of property and equipment of $33.8 million, a product milestone payment of $2.0 million associated with the first product sale of LUXTURNA and a payment of $0.3 million related to a license agreement.

Net cash used in investing activities for the year ended December 31, 2017, was $207.7 million, consisting of net purchases of marketable securities of $189.9 million, purchases of property and equipment of $9.7 million and payments related to our license agreements of $8.2 million.

Net cash used in investing activities for the year ended December 31, 2016, was $285.5 million, consisting of net purchases of marketable securities of $259.9 million and $11.1 million for the investment in the Selecta License Agreement entered into in December 2016. In addition, $8.5 million was used for costs related to the purchase of property and equipment and $5.9 million for the acquisition of Genable, net of cash acquired.

Net cash provided by financing activities

Net cash provided by financing activities for the year ended December 31, 2018, was $63.0 million, which consisted of $50.0 million in proceeds from long-term debt, $15.1 million in proceeds from the exercise of stock options and $1.6 million of proceeds from the issuance of common stock under our employee stock purchase plan. These were offset by $3.4 million for our repurchase of common stock for tax withholding obligations on restricted stock that vested during 2018 and $0.3 million in payments of long-term debt.

Net cash provided by financing activities for the year ended December 31, 2017, was $400.3 million, which consisted of $379.9 million of net proceeds from our follow-on public offering in August 2017, $20.7 million from the exercise of stock options and $0.6 million of proceeds from the issuance of common stock under our employee stock purchase plan, offset by $0.7 million for our repurchase of stock for tax withholding obligations on restricted stock that vested during 2017 and $0.3 million in payments of long-term debt.

Net cash provided by financing activities for the year ended December 31, 2016, was $131.4 million, which consisted of $127.6 million of net proceeds from our follow-on public offering in June 2016, $2.6 million in proceeds from the exercise of stock options, $1.6 million in proceeds from long-term debt and $0.3 million in proceeds from the issuance of common stock under our employee stock purchase plan, offset by expenses of $0.7 million paid in the first quarter of 2016 related to our follow-on offering in December 2015 and payments on long-term debt.

Funding requirements

We expect our expenses to increase in connection with our ongoing activities, particularly as we continue to commercialize LUXTURNA, continue research and development, continue and initiate clinical trials and seek regulatory approvals for our product candidates.

The expected use of our cash, cash equivalents and marketable securities of $548.3 million as of December 31, 2018 represents our intentions based upon our current plans and business conditions, which could change in the future as our plans and business conditions evolve. The amounts and timing of our actual expenditures may vary significantly depending on numerous factors, including the progress of our development programs, the status of, and results from, clinical trials, the potential need to conduct additional clinical trials to obtain approval of our product candidates for all intended indications, the timing and outcome of regulatory filings and actions, commercialization of approved products, as well as any technology acquisitions or additional collaborations into which we may enter with third parties for our product candidates and any unforeseen cash needs. As a result, our management retains broad discretion over the allocation of our existing cash and cash equivalents, and marketable securities.

Based on our planned use of our cash and cash equivalents and marketable securities, we estimate that such funds will be sufficient to enable us to continue to commercialize LUXTURNA, complete our Phase 1/2 trials for *SPK-7001* and *SPK-8011*, initiate the Phase 3 run-in trial for *SPK-8011*, advance certain of our other pipeline product candidates and fund our operating expenses and capital expenditure requirements into 2021. The foregoing

estimate does not contemplate the achievement of any additional milestones under our collaborations with Pfizer and Novartis. Moreover, we have based this estimate on assumptions that may prove to be wrong, and we could use our available capital resources sooner than we currently expect.

Table of Contents

Contractual obligations

The following table summarizes our contractual obligations as of December 31, 2018:

	Payments due by period (in thousands)				
	Total	Less than 1 year	1-3 years	3-5 years	More than 5 years
Operating leases (1)	$126,682	$8,102	$21,117	$19,384	$78,079
Long-term debt obligations	50,912	4,822	12,590	33,500	—
Total (2)	$177,594	$12,924	$33,707	$52,884	$78,079

(1) Operating lease obligations primarily reflect our obligation to make payments in connection with leases for our corporate headquarters and other manufacturing facilities.

(2) This table does not include: (a) any milestone payments which may become payable to third parties under license agreements as the timing and likelihood of such payments are not known with certainty; (b) any royalty payments to third parties as the amounts, timing and likelihood of such payments are not known with certainty; and (c) contracts that are entered into in the ordinary course of business which are not material in the aggregate in any period presented above.

Off-balance sheet arrangements

We did not have, during the periods presented, and we do not currently have, any off-balance sheet arrangements, as defined under applicable Securities and Exchange Commission (SEC) rules.

Recent accounting pronouncements

In February 2016, the Financial Accounting Standards Board (FASB) issued Accounting Standards Update (ASU) 2016-02, *Leases*. ASU 2016-02 requires lessees to apply a two-method approach, classifying leases as either finance or operating leases based on the principle of whether or not the lease is effectively a financed purchase. This classification will determine whether lease expense is recognized based on an effective interest method or on a straight line basis over the term of the lease, respectively. Lessees are also required to record a right-of-use (ROU) asset and a lease liability for all leases with a term greater than 12 months. Leases with a term of 12 months or less will be accounted for similar to existing guidance for operating leases. ASU 2016-02 is effective for interim and annual periods beginning after December 15, 2018. We have elected to adopt the standard using a modified retrospective transition approach. We expect the adoption of the standard to have a material impact on our consolidated balance sheet, which will result in the removal of the built to suit asset and liability recorded at December 31, 2018, and the recognition of ROU assets and lease liabilities of approximately $40.0 million to $50.0 million at January 1, 2019.

In May 2014, the FASB issued a new standard, ASC 606, regarding the accounting for, and disclosures of, revenue recognition, with an effective date for annual and interim periods beginning after December 15, 2017. ASC 606 provides a single comprehensive model for accounting for revenue from contracts with customers. The model requires that revenue recognized reflect the actual consideration to which the entity expects to be entitled in exchange for the goods or services defined in the contract, including in situations with multiple performance obligations. The allowable adoption methods are the full retrospective method, which requires the standard to be applied to each prior period presented, or the modified retrospective method which requires the cumulative effect of adoption to be recognized as an adjustment to opening retained earnings in the period of adoption. We adopted ASC 606 using the modified retrospective method and the adoption had no cumulative adjustment to our consolidated financial statements as it relates to the Pfizer collaboration agreement discussed in Note 16 to the consolidated financial statements. For the year ended December 31, 2018, there was no impact from the adoption of ASC 606 that resulted in a different revenue recognition amount than under the prior revenue recognition guidance in effect during 2017.

In January 2016, the FASB issued ASU 2016-01, *Financial Instruments-Overall: Recognition and Measurement of Financial Assets and Financial Liabilities*. ASU 2016-01 changes accounting for equity investments, financial liabilities under the fair value option, and presentation and disclosure requirements for financial instruments. ASU 2016-01 does not apply to equity investments in consolidated subsidiaries or those accounted for under the equity

method of accounting. In addition, the FASB clarified guidance related to the valuation allowance assessment when recognizing deferred tax assets resulting from unrealized losses on available-for-sale debt securities. Equity investments with readily determinable fair values will be measured at fair value with changes in fair value recognized in net income. Companies have the option to either measure equity investments without readily determinable fair values at fair value or at cost, adjusted for changes in observable prices, minus impairment. Changes in measurement under either alternative will be recognized in net income. Companies that elect the fair

Table of Contents

value option for financial liabilities must recognize changes in fair value related to instrument-specific credit risk in other comprehensive income. Companies must assess valuation allowances for deferred tax assets related to available-for-sale debt securities in combination with their other deferred tax assets. We adopted this guidance effective January 1, 2018, resulting in a reclassification of $5.0 million from accumulated other comprehensive loss to accumulated deficit, related to the unrecognized loss on our investment in Selecta.

In August 2017, the FASB issued ASU 2017-12, *Derivatives and Hedging: Targeted Improvements to Accounting for Hedging Activities*, which improves the financial reporting of hedging relationships to better portray the economic results of an entity's risk management activities in its financial statements and make certain targeted improvements to simplify the application of the hedge accounting guidance in current U.S. GAAP. The amendments in this update better align an entity's risk management activities and financial reporting for hedging relationships through changes to both the designation and measurement guidance for qualifying hedging relationships and the presentation of hedge results. The effective date for the standard is for fiscal years beginning after December 15, 2018. We elected to early adopt this ASU in the third quarter of 2018. The adoption of this guidance did not have a material impact on our consolidated financial statements. See Note 11 for a discussion of our derivatives.

Item 7A. Quantitative and Qualitative Disclosures About Market Risk

We are exposed to market risk related to changes in interest rates. As of December 31, 2018, we had cash and cash equivalents, restricted cash and marketable securities, including our investment in Selecta, of $601.3 million, primarily invested in U.S. government agency and corporate securities, certificates of deposit and money market accounts. We have policies requiring us to invest in the securities of high-quality issuers, limit our exposure to any individual issuer and ensure adequate liquidity. Our primary exposure to market risk is interest rate sensitivity, which is affected by changes in the general level of U.S. interest rates. Our marketable securities are subject to interest rate risk and will fall in value if market interest rates increase. If market interest rates were to increase immediately and uniformly by 100 basis points from levels at December 31, 2018, the net fair value of our marketable securities would have resulted in a hypothetical decline of approximately $4.1 million.

Item 8. Financial Statements and Supplementary Data

Our consolidated financial statements, together with the report of our independent registered public accounting firm, appear on pages F-1 through F-30 of this Annual Report of Form 10-K.

Item 9. Changes in and Disagreements with Accountants on Accounting and Financial Disclosure

None.

Item 9A. Controls and Procedures

Evaluation of disclosure controls and procedures

Our management, with the participation of our Chief Executive Officer and Chief Financial Officer, evaluated the effectiveness of our disclosure controls and procedures as of December 31, 2018. The term “disclosure controls and procedures,” as defined in Rules 13a-15(e) and 15d-15(e) under the Exchange Act, means controls and other procedures of a company that are designed to ensure that information required to be disclosed by a company in the reports that it files or submits under the Exchange Act is recorded, processed, summarized and reported, within the time periods specified in the Securities and Exchange Commission’s rules and forms. Disclosure controls and procedures include, without limitation, controls and procedures designed to ensure that information required to be disclosed by a company in the reports that it files or submits under the Exchange Act is accumulated and communicated to the company’s management, including its principal executive and principal financial officers, as appropriate to allow timely decisions regarding required disclosure. Management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving their objectives and management necessarily applies its judgment in evaluating the cost-benefit relationship of possible

controls and procedures. Based on the evaluation of our disclosure controls and procedures as of December 31, 2018, our Chief Executive Officer and Chief Financial Officer concluded that, as of such date, our disclosure controls and procedures were effective at the reasonable assurance level.

Management's report on internal control over financial reporting

Our management is responsible for establishing and maintaining adequate internal control over financial reporting for our company. Internal control over financial reporting is defined in Rule 13a-15(f) or 15d-15(f) promulgated under the Exchange Act as a process designed by, or under the supervision of, the company's principal executive and principal financial officers and

Table of Contents

effected by the company's board of directors, management and other personnel, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles and includes those policies and procedures that: (i) pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of the assets of the company; (ii) provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that receipts and expenditures of our company are being made only in accordance with authorizations of management and directors of the company; and (iii) provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use, or disposition of our company's assets that could have a material effect on the financial statements.

Internal control over financial reporting is designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements prepared for external purposes in accordance with generally accepted accounting principles. Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Also, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

Our management, with the participation of our Chief Executive Officer and Chief Financial Officer, assessed the effectiveness of our internal control over financial reporting as of December 31, 2018. In making this assessment, our management used the criteria set forth in the *Internal Control-Integrated Framework (2013)* issued by the Committee of Sponsoring Organizations of the Treadway Commission. Based on its assessment, management concluded that our internal control over financial reporting was effective as of December 31, 2018 based on those criteria.

Our independent registered public accounting firm, which has audited the consolidated financial statements included in this Annual Report on Form 10-K, has also issued an audit report on the effectiveness of our internal control over financial reporting as of December 31, 2018. Their report appears on page F-2 of this Annual Report on Form 10-K.

Changes in internal control over financial reporting

With our increased commercialization efforts for LUXTURNA, we have implemented internal controls around inventory and cost of goods sold. There have been no other changes in our internal control over financial reporting (as defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act) that occurred during the current quarter ended December 31, 2018 that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

Item 9B. Other Information

None.

Table of Contents

PART III

Item 10. Directors, Executive Officers and Corporate Governance

The information required by this Item is incorporated by reference from the discussion responsive thereto contained in an amendment to this Form 10-K or in the Proxy Statement for our 2019 Annual Meeting of Stockholders, either of which we intend to file with the SEC within 120 days of the end of the fiscal year to which this Annual Report on Form 10-K relates.

Item 11. Executive Compensation

The information required by this Item is incorporated by reference from the discussion responsive thereto contained in an amendment to this Form 10-K or in the Proxy Statement for our 2019 Annual Meeting of Stockholders, either of which we intend to file with the SEC within 120 days of the end of the fiscal year to which this Annual Report on Form 10-K relates.

Item 12. Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters

The information required by this Item is incorporated by reference from the discussion responsive thereto contained in an amendment to this Form 10-K or in the Proxy Statement for our 2019 Annual Meeting of Stockholders, either of which we intend to file with the SEC within 120 days of the end of the fiscal year to which this Annual Report on Form 10-K relates.

Item 13. Certain Relationships and Related Transactions, and Director Independence

The information required by this Item is incorporated by reference from the discussion responsive thereto contained in an amendment to this Form 10-K or in the Proxy Statement for our 2019 Annual Meeting of Stockholders, either of which we intend to file with the SEC within 120 days of the end of the fiscal year to which this Annual Report on Form 10-K relates.

Item 14. Principal Accountant Fees and Services

The information required by this Item is incorporated by reference from the discussion responsive thereto contained in an amendment to this Form 10-K or in the Proxy Statement for our 2019 Annual Meeting of Stockholders, either of which we intend to file with the SEC within 120 days of the end of the fiscal year to which this Annual Report on Form 10-K relates.

PART IV

Item 15. Exhibits, Financial Statement Schedules

The consolidated financial statements listed in the Index to the Financial Statements beginning on page F-1 are filed as part of this Annual Report on Form 10-K.

No financial statement schedules have been filed as part of this Annual Report on Form 10-K because they are not applicable, not required or because the information is otherwise included in our consolidated financial statements or notes thereto.

96

Table of Contents

The following is a list of the Company's Exhibits:

Exhibit Number	Description of Exhibit	Incorporated by Reference				Filed/Furnished Herewith
		Form	File Number	Date of Filing	Exhibit Number	
2.1	Agreement and Plan of Merger, dated as of February 22, 2019, among Spark Therapeutics, Inc., Roche Holdings, Inc. and 022019 Merger Subsidiary, Inc.	8-K	001-36819	2/25/2019	2.1	
3.1	Restated Certificate of Incorporation of the Registrant	8-K	001-36819	2/6/2015	3.1	
3.2	Amended and Restated By-Laws of the Registrant	8-K	001-36819	2/6/2015	3.2	
3.3	Amendment to Amended and Restated By-laws of Spark Therapeutics, Inc. dated February 22, 2019	8-K	001-36819	2/25/2019	3.1	
4.1	Specimen Stock Certificate evidencing the shares of common stock	S-1/A	333-201318	1/20/2015	4.1	
4.2	Investors' Rights Agreement dated as of May 23, 2014	S-1	333-201318	12/30/2014	4.2	
10.1+	2014 Stock Incentive Plan	S-1	333-201318	12/30/2014	10.1	
10.2+	Form of Incentive Stock Option Agreement under 2014 Stock Incentive Plan	S-1	333-201318	12/30/2014	10.2	
10.3+	Form of Nonstatutory Stock Option Agreement under 2014 Stock Incentive Plan	S-1	333-201318	12/30/2014	10.3	
10.4+	Form of Restricted Stock Agreement under 2014 Stock Incentive Plan	S-1	333-201318	12/30/2014	10.4	
10.5+	2015 Stock Incentive Plan	S-1/A	333-201318	1/20/2015	10.5	
10.6+	Form of Incentive Stock Option Agreement under 2015 Stock Incentive Plan	S-1/A	333-201318	1/20/2015	10.6	
10.7+	Form of Nonstatutory Stock Option Agreement under 2015 Stock Incentive Plan	S-1/A	333-201318	1/20/2015	10.7	
10.8+	2015 Employee Stock Purchase Plan	S-1/A	333-201318	1/20/2015	10.8	
10.9†	License Agreement dated October 14, 2013 between the Registrant and The Children's Hospital of Philadelphia, as amended	S-1	333-201318	12/30/2014	10.8	
10.10†	Technology Assignment Agreement dated October 14,	S-1	333-201318	12/30/2014	10.9	

	2013 between the Registrant and The Children's Hospital of Philadelphia				
10.11†	Master Research Services Agreement dated October 14, 2013 between the Registrant and The Children's Hospital of Philadelphia	S-1	333-201318	12/30/2014	10.10
10.12†	License Agreement dated October 14, 2013 between the Registrant and the University of Iowa Research Foundation, as amended	S-1	333-201318	12/30/2014	10.12
10.13†	License Agreement dated December 6, 2014 between the Registrant and Pfizer Inc.	S-1	333-201318	12/30/2014	10.18

Table of Contents

Exhibit Number	Description of Exhibit	Incorporated by Reference				Filed/Furnished Herewith
		Form	File Number	Date of Filing	Exhibit Number	
10.14†	Lease Agreement, dated as of March 31, 2014, between the Registrant and Wexford-UCSC 3737, LLC	S-1	333-201318	12/30/2104	10.19	
10.15+	Common Share Membership Agreement between the Registrant and Katherine A. High	S-1	333-201318	12/30/2014	10.21	
10.16+	Employment Agreement between the Registrant and Jeffrey D. Marrazzo	S-1/A	333-201318	1/20/2015	10.21	
10.17+	Form of Indemnification Agreement between the Registrant and each of the executive officers and directors	S-1/A	333-201318	1/20/2015	10.26	
10.18†	Amendment No. 2, dated March 23, 2015 to License Agreement dated October 14, 2013 between the Registrant and the University of Iowa Research Foundation, as amended	10-Q	001-36819	5/11/2015	10.1	
10.19	Amendment No.1 dated August 5, 2015 to the Services Agreement dated December 26, 2013 between the Registrant and the Children's Hospital of Philadelphia	10-Q	001-36819	11/6/2015	10.1	
10.20†	Amendment No.4 dated October 8, 2015 to the License Agreement dated October 14, 2013 between the Registrant and the Children's Hospital of Philadelphia	10-Q	001-36819	11/6/2015	10.2	
10.21†	License Agreement dated November 23, 2015 between the Registrant and the The Children's Hospital of Philadelphia	8-K	001-36819	11/23/2015	99.1	
10.22†	Amended and Restated Patent License Agreement dated December 31, 2015, between the Registrant and The Trustees of the University of Pennsylvania	10-K	001-36819	3/14/2016	10.31	
10.23+	Amendment, dated January 5, 2016 to the Employment Agreement between the Registrant and Jeffrey D. Marrazzo	10-K	001-36819	3/14/2016	10.32	
10.24†	Amendment No. 3, dated January 6, 2016 to License Agreement dated October 14, 2013 between the Registrant and the University of Iowa Research Foundation	10-K	001-36819	3/14/2016	10.33	
10.25†	Amendment No. 1, dated March 10, 2016 to Master Research Services Agreement dated October 14, 2013	10-K	001-36819	3/14/2016	10.34	

	between the Registrant and The Children's Hospital of Philadelphia				
10.26	Lease Agreement, dated as of February 1, 2016, between the Registrant and Wexford-UCSC II, LP	10-K	001-36819	3/14/2016	10.35
10.27†	Amendment dated March 10, 2016, to the License Agreement dated November 23, 2015 between the Registrant and The Children's Hospital of Philadelphia	10-K	001-36819	3/14/2016	10.36
10.28†	Amendment No. 1, dated June 9, 2016, to the License Agreement dated December 6, 2014 between the Registrant and Pfizer	10-Q	001-36819	8/10/2016	10.1

Table of Contents

Exhibit Number	Description of Exhibit	Incorporated by Reference				Filed/Furnished Herewith
		Form	File Number	Date of Filing	Exhibit Number	
10.29+	Form of Employment Agreement for Executive Officer	10-Q	001-36819	8/10/2016	10.2	
10.30†	License and Option Agreement, dated December 2, 2016 between the Registrant and Selecta Biosciences, Inc.	10-K	001-36819	2/28/2017	10.32	
10.31†	Letter Agreement, dated June 6, 2017, amending the License and Option Agreement dated December 2, 2016 between the Registrant and Selecta Biosciences, Inc.	10-Q	001-36819	8/2/2017	10.1	
10.32	Lease Agreement, dated as of November 20, 2017, between the Registrant and Brandywine 3025 Market, LP	10-K	001-36819	2/27/2018	10.34	
10.33†	Amendment No. 2, dated November 6, 2017, to the License Agreement dated December 6, 2014 between the Registrant and Pfizer	10-K	001-36819	2/27/2018	10.35	
10.34†	Supply Agreement, dated January 24, 2018, between the Registrant and Novartis Pharma AG	10-K	001-36819	2/27/2018	10.36	
10.35†	License and Commercialization Agreement dated January 24, 2018 between the Registrant and Novartis Pharma AG	10-K	001-36819	2/27/2018	10.37	
10.36†	Manufacture and Supply Agreement, dated February 16, 2018, between the Registrant and Pfizer	10-Q	001-36819	5/8/2018	10.3	
10.37	Asset Purchase Agreement, dated April 30, 2018 between the Registrant and Jazz Pharmaceuticals Ireland Limited	10-Q	001-36819	8/8/2018	10.1	
10.38†	Dedicated Manufacturing and Commercial Supply Agreement, dated August 3, 2018, between the Registrant and Brammer Bio MA, LLC	10-Q	001-36819	11/6/2018	10.1	
10.39	Credit Agreement, dated July 3, 2018, between the Registrant and Wells Fargo Bank, National Association	10-Q	001-36819	11/6/2018	10.2	
10.40	Cash Collateral Agreement, dated July 3, 2018, between the Registrant and Wells Fargo Bank, National Association	10-Q	001-36819	11/6/2018	10.3	
10.41	Amendment No. 1, dated October 1, 2018, to the Lease Agreement dated November 20, 2017 between the Registrant and Brandywine 3025 Market, LP					X
10.42††	License Agreement Amendment dated March 10, 2016 (effective November 23, 2015) amending and superseding					X

	the License Agreement between the Company and the Children's Hospital of Philadelphia dated November 23, 2015				
21.1	Subsidiaries of the Registrant				X

Incorporated by Reference

99

Table of Contents

Exhibit Number	Description of Exhibit	Form	File Number	Date of Filing	Exhibit Number	Filed/Furnished Herewith
23.1	Consent of KPMG LLP					X
31.1	Certification of principal executive officer pursuant to Rule 13a-14(a)/15d-14(a) of the Securities Exchange Act of 1934, as amended					X
31.2	Certification of principal financial officer pursuant to Rule 13a-14(a)/15d-14(a) of the Securities Exchange Act of 1934, as amended					X
32.1	Certification of principal executive officer pursuant to 18 U.S.C. §1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002					X
32.2	Certification of principal financial officer pursuant to 18 U.S.C. §1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002					X
101	The following materials from the Company's Annual Report on Form 10-K for the year ended December 31, 2018, formatted in XBRL (eXtensible Business Reporting Language): (i) Consolidated Balance Sheets as of December 31, 2017 and December 31, 2018, (ii) Consolidated Statements of Operations and Other Comprehensive Income (Loss) for the years ended December 31, 2016, 2017 and 2018, (iii) Consolidated Statements of Stockholders' Equity for the years ended December 31, 2016, December 31, 2017 and December 31, 2018 (iv) Consolidated Statements of Cash Flows for the years ended December 31, 2016, 2017 and 2018 and (v) Notes to Audited Consolidated Financial Statements.					X

† Confidential treatment has been granted as to certain portions of the exhibit. Confidential materials omitted and filed separately with the Securities and Exchange Commission.

†† Confidential treatment requested as to portions of the exhibit. Confidential materials omitted and filed separately with the Securities and Exchange Commission.

+ Management contract or compensatory plan or arrangement filed in response to Item 15(a)(3) of the Instructions to the Annual Report on Form 10-K.

Item 16. Form 10-K Summary

None.

100

Table of Contents

Spark Therapeutics, Inc.
Index to consolidated financial statements

Table of Contents

Report of Independent Registered Public Accounting Firm

To the Stockholders and Board of Directors
Spark Therapeutics, Inc.:

Opinions on the Consolidated Financial Statements and Internal Control Over Financial Reporting

We have audited the accompanying consolidated balance sheets of Spark Therapeutics, Inc. and subsidiaries (the Company) as of December 31, 2017 and 2018, the related consolidated statements of operations and comprehensive income (loss), stockholders' equity, and cash flows for each of the years in the three-year period ended December 31, 2018, and the related notes (collectively, the consolidated financial statements). We also have audited the Company's internal control over financial reporting as of December 31, 2018, based on criteria established in *Internal Control - Integrated Framework (2013)* issued by the Committee of Sponsoring Organizations of the Treadway Commission.

In our opinion, the consolidated financial statements referred to above present fairly, in all material respects, the financial position of the Company as of December 31, 2017 and 2018, and the results of its operations and its cash flows for each of the years in the three-year period ended December 31, 2018, in conformity with U.S. generally accepted accounting principles. Also in our opinion, the Company maintained, in all material respects, effective internal control over financial reporting as of December 31, 2018, based on criteria established in *Internal Control - Integrated Framework (2013)* issued by the Committee of Sponsoring Organizations of the Treadway Commission.

Basis for Opinions

The Company's management is responsible for these consolidated financial statements, for maintaining effective internal control over financial reporting, and for its assessment of the effectiveness of internal control over financial reporting, included in the accompanying Management's report on internal control over financial reporting. Our responsibility is to express an opinion on the Company's consolidated financial statements and an opinion on the Company's internal control over financial reporting based on our audits. We are a public accounting firm registered with the Public Company Accounting Oversight Board (United States) (PCAOB) and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audits in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audits to obtain reasonable assurance about whether the consolidated financial statements are free of material misstatement, whether due to error or fraud, and whether effective internal control over financial reporting was maintained in all material respects.

Our audits of the consolidated financial statements included performing procedures to assess the risks of material misstatement of the consolidated financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the consolidated financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the consolidated financial statements. Our audit of internal control over financial reporting included obtaining an understanding of internal control over financial reporting, assessing the risk that a material weakness exists, and testing and evaluating the design and operating effectiveness of internal control based on the assessed risk. Our audits also included performing such other procedures as we considered necessary in the circumstances. We believe that our audits provide a reasonable basis for our opinions.

Definition and Limitations of Internal Control Over Financial Reporting

A company's internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles. A company's internal control over financial reporting includes those policies and procedures that (1) pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of the assets of the company; (2) provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that receipts and expenditures of the company are being made only in accordance

with authorizations of management and directors of the company; and (3) provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use, or disposition of the company's assets that could have a material effect on the financial statements.

Table of Contents

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Also, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

/s/ KPMG LLP

We have served as the Company's auditor since 2014.

Philadelphia, Pennsylvania

February 28, 2019

Table of Contents

Spark Therapeutics, Inc.
Consolidated balance sheets
(in thousands, except share and per share data)

	December 31, 2017	December 31, 2018
Assets		
Current assets:		
Cash and cash equivalents	$ 96,748	$ 95,247
Marketable securities	423,419	358,359
Trade and other receivables	7,906	47,385
Inventory	—	25,637
Prepaid expenses and other current assets	5,093	40,512
Total current assets	533,166	567,140
Restricted cash	—	53,000
Marketable securities	20,035	94,678
Property and equipment, net	61,713	95,998
Goodwill	1,254	1,198
Other assets	628	2,338
Total assets	$ 616,796	$ 814,352
Liabilities and Stockholders' Equity		
Current liabilities:		
Accounts payable	$ 14,183	$ 19,492
Accrued expenses	24,697	34,790
Current portion of long-term debt	312	4,822
Current portion of deferred rent	969	1,365
Current portion of deferred revenue	11,969	—
Current other liabilities	1,557	1,885
Total current liabilities	53,687	62,354
Long-term debt	912	46,090
Long-term deferred rent	8,318	10,885
Long-term deferred revenue	—	160,000
Other liabilities	40,255	38,510
Total liabilities	103,172	317,839
Stockholders' equity:		
Preferred stock, $0.001 par value. Authorized, 5,000,000 shares; no shares issued or outstanding	—	—
Common stock, $0.001 par value. Authorized, 150,000,000 shares; 37,131,626 shares issued and 37,111,404 shares outstanding as of December 31, 2017; 37,764,213 shares issued and 37,686,301 shares outstanding as of December 31, 2018	37	38
Additional paid-in capital	1,026,590	1,091,873
Accumulated other comprehensive loss	(5,914)	(1,050)
Treasury stock, at cost, 20,222 common shares as of December 31, 2017 and 77,912 common shares as of December 31, 2018	(1,226)	(4,661)
Accumulated deficit	(505,863)	(589,687)
Total stockholders' equity	513,624	496,513
Total liabilities and stockholders' equity	$ 616,796	$ 814,352

See accompanying notes to the consolidated financial statements.

Spark Therapeutics, Inc.
Consolidated statements of operations and comprehensive income (loss)
(in thousands, except share and per share data)

	For the year ended December 31,		
	2016	2017	2018
Revenues:			
Product sales, net	$—	$—	$26,973
Contract revenue	20,183	12,066	37,752
Total revenues	20,183	12,066	64,725
Operating expenses:			
Cost of product sales	—	—	1,008
Cost of contract revenue	—	—	6,907
Research and development	86,380	135,160	125,254
Acquired in-process research and development	11,132	8,604	300
Impairment of acquired in-process research and development	—	15,696	—
Selling, general and administrative	48,070	111,124	124,895
Total operating expenses	145,582	270,584	258,364
Loss from operations	(125,399)	(258,518)	(193,639)
Unrealized loss on equity investments	—	—	(5,078)
Interest income, net	1,746	4,073	9,994
Other income	—	—	110,000
Loss before income taxes	(123,653)	(254,445)	(78,723)
Income tax benefit (expense)	—	963	(99)
Net loss	$(123,653)	$(253,482)	$(78,822)
Basic and diluted net loss per common share	$(4.29)	$(7.63)	$(2.11)
Weighted average basic and diluted common shares outstanding	28,804,133	33,242,072	37,366,782
Net loss	$(123,653)	$(253,482)	$(78,822)
Other comprehensive income (loss):			
Unrealized (loss) gain on available-for-sale securities	(801)	(5,163)	586
Unrealized loss on interest rate swap	—	—	(641)
Foreign exchange translation adjustment	7	43	(83)
Total comprehensive loss	$(124,447)	$(258,602)	$(78,960)

See accompanying notes to the consolidated financial statements.

Spark Therapeutics, Inc.
Consolidated statements of stockholders' equity
For the years ended December 31, 2016 and 2017
(in thousands, except share data)

	Common stock		Additional paid-in capital	Accumulated other comprehensive loss	Common stock in treasury		Accumulated deficit	Total
	Shares	Amount			Shares	Amount		
Balance, December 31, 2015	27,082,493	$ 27	$419,792	$ —	9,206	$(553)	$(128,728)	$290,538
Issuance of common stock, net of issuance costs	3,025,000	3	127,563	—	—	—	—	127,566
Issuance of restricted stock	40,000	—	—	—	—	—	—	—
Restricted stock canceled	(2,213)	—	—	—	—	—	—	—
Purchase of common stock under ESPP	8,012	—	340	—	—	—	—	340
Issuance of stock for acquisition	265,000	—	9,151	—	—	—	—	9,151
Exercise of stock options	455,138	1	2,591	—	—	—	—	2,592
Unrealized loss on investments	—	—	—	(801)	—	—	—	(801)
Unrealized gain on foreign currency translation	—	—	—	7	—	—	—	7
Stock-based compensation expense	—	—	24,537	—	—	—	—	24,537
Net loss	—	—	—	—	—	—	(123,653)	(123,653)
Balance, December 31, 2016	30,873,430	31	583,974	(794)	9,206	(553)	(252,381)	330,277
Issuance of common stock, net of issuance costs	5,296,053	5	379,865	—	—	—	—	379,870
Issuance of restricted stock	1,193	—	—	—	—	—	—	—
Restricted stock canceled	(4,107)	—	—	—	—	—	—	—
Purchase of common stock in treasury	—	—	—	—	11,016	(673)	—	(673)
Purchase of common stock under ESPP	11,804	—	646	—	—	—	—	646
Exercise of stock options	953,253	1	20,732	—	—	—	—	20,733
Unrealized loss on investments	—	—	—	(5,163)	—	—	—	(5,163)
Unrealized gain on foreign currency translation	—	—	—	43		—	—	43
Stock-based compensation expense	—	—	41,373	—	—	—	—	41,373
Net loss	—	—	—	—	—	—	(253,482)	(253,482)
Balance, December 31, 2017	37,131,626	$ 37	$1,026,590	$ (5,914)	20,222	$(1,226)	$(505,863)	$513,624

See accompanying notes to the consolidated financial statements.

Spark Therapeutics, Inc.
Consolidated statement of stockholders' equity
For the year ended December 31, 2018
(in thousands, except share data)

	Common stock		Additional paid-in capital	Accumulated other comprehensive loss	Common stock in treasury		Accumulated deficit	Total
	Shares	Amount			Shares	Amount		
Balance, December 31, 2017	37,131,626	$ 37	$1,026,590	$ (5,914)	20,222	$(1,226)	$(505,863)	$513,624
Reclassification of unrealized loss on equity investment to accumulated deficit	—	—	—	5,002	—	—	(5,002)	—
Issuance of restricted stock	172,868	—	—	—	—	—	—	—
Restricted stock canceled	(25,000)	—	—	—	—	—	—	—
Purchase of common stock in treasury	—	—	—	—	57,690	(3,435)	—	(3,435)
Purchase of common stock under ESPP	30,814	—	1,567	—	—	—	—	1,567
Exercise of stock options	453,905	1	15,130	—	—	—	—	15,131
Unrealized gain on investments	—	—	—	586	—	—	—	586
Unrealized loss on interest rate swap	—	—	—	(641)	—	—	—	(641)
Unrealized loss on foreign currency translation	—	—	—	(83)	—	—	—	(83)
Stock-based compensation expense	—	—	48,586	—	—	—	—	48,586
Net loss	—	—	—	—	—	—	(78,822)	(78,822)
Balance, December 31, 2018	37,764,213	$ 38	$1,091,873	$ (1,050)	77,912	$(4,661)	$(589,687)	$496,513

See accompanying notes to the consolidated financial statements.

Spark Therapeutics, Inc.
Consolidated statements of cash flows
(in thousands)

	For the year ended December 31,		
	2016	**2017**	**2018**
Cash flows from operating activities:			
Net loss	$(123,653)	$(253,482)	$(78,822)
Adjustments to reconcile net loss to net cash used in operating activities:			
Non-cash rent income	(530)	(531)	(2,490)
Depreciation and amortization expense	3,634	4,860	6,918
Loss on disposal of property and equipment	101	32	103
Acquired in-process research and development	11,132	8,604	300
Stock-based compensation expense	24,537	41,373	48,586
Impairment of acquired in-process research and development	—	15,696	—
Non-cash income tax benefit	—	(1,013)	—
Gain from sale of priority review voucher	—	—	(110,000)
Unrealized loss on equity investments	—	—	5,078
Non-cash interest income	—	(127)	(1,112)
Changes in operating assets and liabilities:			
Inventory	—	—	(25,637)
Prepaid expenses and other assets	(264)	(3,157)	(35,333)
Trade and other receivables	(235)	8,857	(39,501)
Accounts payable and accrued expenses	10,018	12,981	8,703
Deferred rent	—	1,610	3,972
Deferred revenue	(5,182)	2,934	148,031
Other liabilities	—	6,827	641
Net cash used in operating activities	(80,442)	(154,536)	(70,563)
Cash flows from investing activities:			
Proceeds from sale of priority review voucher	—	—	110,000
Payment for license agreement	—	—	(2,000)
Purchase of acquired in-process research and development	(11,132)	(8,217)	(300)
Payment for acquisition, net of cash acquired	(5,911)	—	—
Purchase of marketable securities	(279,945)	(441,486)	(530,989)
Proceeds from maturities of marketable securities	20,000	251,625	516,273
Purchase of property and equipment	(8,532)	(9,654)	(33,821)
Net cash (used in) provided by investing activities	(285,520)	(207,732)	59,163
Cash flows from financing activities:			
Proceeds from exercise of options	2,592	20,733	15,131
Purchase of treasury stock	—	(673)	(3,435)
Proceeds from public offerings of common stock, net	126,909	379,870	—
Proceeds from issuance of common stock under ESPP	340	646	1,567
Proceeds from long-term debt	1,550	—	50,000
Payments on long-term debt	(25)	(302)	(312)
Net cash provided by financing activities	131,366	400,274	62,951
Effect of exchange rate changes on cash and cash equivalents and restricted cash	(12)	(181)	(52)
Net (decrease) increase in cash and cash equivalents and restricted cash	(234,608)	37,825	51,499
Cash and cash equivalents and restricted cash, beginning of year	293,531	58,923	96,748
Cash and cash equivalents and restricted cash, end of year	$58,923	$96,748	$148,247

See accompanying notes to the consolidated financial statements.

Spark Therapeutics, Inc.
Consolidated statements of cash flows
(in thousands)

	For the year ended December 31,		
	2016	2017	2018
Supplemental disclosure of cash flow information:			
Property and equipment purchases included in accounts payable and accrued expenses	$682	$2,789	$9,518
One Drexel Plaza lease cost included in other liabilities	$—	$34,986	$503

See accompanying notes to the consolidated financial statements.

Spark Therapeutics, Inc.
Notes to consolidated financial statements

(1) Background

Spark Therapeutics, Inc. was formed on March 13, 2013 in the state of Delaware as AAVenue Therapeutics, LLC and amended its Certificate of Formation in October 2013 to change its name to Spark Therapeutics LLC. In May 2014, the Company converted from a limited liability company (LLC) to a C corporation, Spark Therapeutics, Inc. (the Company). The Company is a gene therapy company, seeking to transform the lives of patients suffering from debilitating genetic diseases by developing potentially one-time, life-altering treatments. The Company operates in one segment and has its principal offices in Philadelphia, Pennsylvania.

In December 2017, the U.S. Food and Drug Administration, or FDA, approved LUXTURNA™ (voretigene neparvovec-rzyl) for the treatment of patients with viable retinal cells and confirmed biallelic *RPE65* mutation-associated retinal dystrophy.

(2) Development-stage risks

The Company has incurred net losses and negative cash flows from operations since inception and expects to incur net losses for the foreseeable future. The Company had an accumulated deficit of $589.7 million as of December 31, 2018. The Company anticipates incurring additional losses until such time, if ever, that it can generate significant sales of LUXTURNA and its other product candidates in development. Additional financing may be needed by the Company to fund its operations and to commercially develop its other product candidates.

The Company's future operations are highly dependent on a combination of factors, including: (i) the success of its research and development; (ii) regulatory approval of the Company's proposed future products; (iii) the continued success of the commercialization of LUXTURNA; (iv) the timely and successful completion of additional financing; and (v) the development of competitive therapies by other biotechnology and pharmaceutical companies.

(3) Summary of significant accounting policies

(a) Use of estimates

The preparation of consolidated financial statements in conformity with U.S. generally accepted accounting principles (GAAP) requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities and disclosure of contingent assets and liabilities at the date of the consolidated financial statements and the reported amounts of revenues and expenses during the reporting period. Actual results could differ from such estimates.

(b) Principles of consolidation

The accompanying consolidated financial statements include the accounts of the Company and its wholly-owned subsidiaries: Spark Therapeutics Ireland Limited, Spark Therapeutics UK Limited, Spark Therapeutics Argentina Limited, Spark Therapeutics Switzerland Limited, Spark Therapeutics Germany Limited and Spark Therapeutics France Limited. All intercompany balances and transactions have been eliminated in consolidation.

(c) Fair value of financial instruments

Management believes that the carrying amounts of the Company's financial instruments, including cash equivalents, trade and other receivables, accounts payable and accrued expenses, approximate fair value due to the short-term nature of those instruments. Management believes the carrying value of debt approximates fair value as the interest rates are reflective of the rate the Company could obtain on debt with similar terms and conditions.

(d) Cash and cash equivalents

The Company considers all highly liquid investments that have maturities of three months or less when acquired to be cash equivalents. Cash equivalents as of December 31, 2017 and 2018 consisted of money market funds.

Spark Therapeutics, Inc.
Notes to consolidated financial statements

(e) Marketable securities
The Company classifies its marketable security investments as available-for-sale securities and the securities are stated at fair value. At December 31, 2018, the balance in the Company's accumulated other comprehensive loss included activity related to the Company's available-for-sale marketable securities. There were no material realized gains or losses recognized on the maturity of available-for-sale securities during the year ended December 31, 2018 and, as a result, the Company did not reclassify any amount out of accumulated other comprehensive loss for the same period. In addition, as part of the license and stock purchase agreements entered into with Selecta Biosciences, Inc. (Selecta) (Note 16), the Company purchased common shares of Selecta. The investment is classified as available-for-sale and is stated at fair value, and beginning in 2018 changes in fair value are recognized in the consolidated statements of operations and comprehensive income (loss).

(f) Trade and other receivables
Trade accounts receivable are recorded at gross value, and reserves for other sales-related allowances, such as discounts, rebates, services and insurance co-pay assistance, are included in accrued expenses on the Company's consolidated balance sheets.

(g) Inventory
Inventory is stated at the lower of cost or net realizable value and consists of those costs incurred following FDA approval of LUXTURNA. Cost is determined using the first-expired, first-out (FEFO) method. The Company reserves for potentially excess, dated or obsolete inventories based on an analysis of inventory on hand compared to forecasts of future sales. Based on management's assessment, no such inventory reserve is necessary as of December 31, 2018.

(h) Property and equipment
Property and equipment consists of computer and laboratory equipment, software, office equipment, furniture and leasehold improvements and is recorded at cost. Maintenance and repairs that do not improve or extend the lives of the respective assets are expensed to operations as incurred. Upon disposal, retirement or sale, the related cost and accumulated depreciation are removed from the accounts and any resulting gain or loss is included in the results of operations. Property and equipment are depreciated on a straight-line basis over their estimated useful lives. The Company uses a life of three years for computer equipment and software, five years for laboratory and office equipment and seven years for furniture. Leasehold improvements are amortized over the shorter of the lease term or the estimated useful life of the asset.
The Company reviews long-lived assets, such as property and equipment, for impairment when events or changes in circumstances indicate the carrying value of the assets may not be recoverable. Recoverability is measured by comparison of the book values of the assets to estimated undiscounted future cash flows that the assets are expected to generate. If the carrying amount of an asset exceeds its estimated future cash flows, then an impairment charge is recognized for the amount by which the carrying value of the asset exceeds the fair value of the asset. No impairment charges have been recorded since inception.

(i) Net product sales
LUXTURNA is distributed in the United States through two distribution models: (1) the traditional buy-and-bill model where the treatment center purchases and pays for the product and then submits a claim to the payer; and (2) the Company's innovative contracting and distribution model, branded Spark PATH (Pioneering Access to Healthcare), which includes options for direct-to-payer contracting and outcomes-based rebates.
The Company's net product sales represent total gross product sales in the United States less allowances for estimated prompt-payment discounts, service fees, rebates and insurance co-payment assistance. Allowances are established based on contractual terms and management's reasonable estimates, as well as the expectation that 100% of the prompt-payment discounts will be earned. Product shipping and handling costs and distributor reporting fees are

included in cost of product sales. The Company evaluated the variable consideration under Accounting Standards Codification (ASC) Topic 606, *Revenue from Contracts with Customers* (ASC 606), as it relates to the outcomes-based method and determined that based on historical clinical data, no rebate reserves were required for the year ended December 31, 2018. All sales are recognized when control is transferred, which follows the Company's verification of a scheduled LUXTURNA treatment.

Spark Therapeutics, Inc.
Notes to consolidated financial statements

The Company's product return policy is to provide non-monetary credit or product replacement. As the product is sold in direct relation to a scheduled treatment, Company management estimates that there is minimal risk of product return, including the risk of product expiration.

(j) Contract revenue

Under certain of the Company's licensing, supply and collaboration agreements, it is entitled to receive payment upon the achievement of contingent milestone events or the performance of obligations. The Company recognizes revenue based on guidance in ASC 606.

Prior to 2018, the Company generated revenue solely through license and collaborative arrangements. In the first quarter of 2018, the Company adopted ASC 606. The adoption of this standard resulted in no cumulative adjustment to the Company's consolidated financial statements.

ASC 606 applies to all contracts with customers, except for contracts that are within the scope of other standards, such as leases, insurance, collaboration arrangements and financial instruments. To determine revenue recognition for arrangements that an entity determines are within the scope of ASC 606, the entity performs the following five steps: (i) identify the contract(s) with a customer; (ii) identify the performance obligations in the contract; (iii) determine the transaction price; (iv) allocate the transaction price to the performance obligations in the contract; and (v) recognize revenue when (or as) the entity satisfies a performance obligation. At contract inception, once the contract is determined to be within the scope of ASC 606, the Company assesses the goods or services promised within each contract and determines those that are performance obligations and assesses whether each promised good or service is distinct. The Company then recognizes as revenue the amount of the transaction price that is allocated to the respective performance obligation when (or as) the performance obligation is satisfied.

Amounts received prior to satisfying the revenue recognition criteria are recorded as deferred revenue on the Company's consolidated balance sheet. Amounts expected to be recognized as revenue in the next 12 months following the balance sheet date are classified as current liabilities.

(k) Research and development and in-process research and development

Research and development costs are expensed as incurred. Research and development expenses consist of internal and external expenses. Internal expenses include employee compensation and overhead. External expenses include development, clinical trials, statistical analysis and report writing and regulatory compliance costs incurred with clinical research organizations and other third-party vendors. At the end of the reporting period, the Company compares payments made to third-party service providers to the estimated progress toward completion of the research or development objectives. Such estimates are subject to change as additional information becomes available. Depending on the timing of payments to the service providers and the progress that the Company estimates has been made as a result of the service provided, the Company may record net prepaid or accrued expense relating to these costs. When the Company is reimbursed by a collaboration partner for work performed, the costs incurred are recorded as research and development expenses and the related reimbursement is recorded as a reduction to research and development expenses.

Upfront and milestone payments made to third parties that perform research and development services on the Company's behalf are expensed as services are rendered. Costs incurred in obtaining technology licenses outside of business combinations are charged to research and development expense as acquired in-process research and development if the technology licensed has not reached technological feasibility and has no alternative future use.

(l) Income taxes

The Company recognizes deferred tax assets and liabilities for temporary differences between the financial reporting basis and the tax basis of its assets and liabilities and the expected benefits of net operating loss and tax credit carryforwards. The impact of changes in tax rates and laws on deferred taxes, if any, is applied during the years in which temporary differences are expected to be settled and net operating losses and tax credits used and is reflected in the consolidated financial statements in the period of enactment. The measurement of deferred tax assets is reduced, if

necessary, if, based on weight of the evidence, it is more likely than not that some, or all, of the deferred tax assets will not be realized. As of December 31, 2017 and 2018, the Company has concluded that a full valuation allowance is necessary for its deferred tax assets.

(m) Stock-based compensation and fair value of stock

The Company accounts for its stock-based compensation awards in accordance with ASC Topic 718, *Compensation-Stock*

Spark Therapeutics, Inc.
Notes to consolidated financial statements

Compensation (ASC 718). ASC 718 requires all stock-based payments to employees, including grants of employee stock options and restricted stock units and modifications to existing stock options, to be recognized in the consolidated statement of operations and comprehensive income(loss) based on their fair values. The Company uses the Black-Scholes option pricing model to determine the fair value of options granted.

The Company's stock-based awards are subject to either service or performance-based vesting conditions. Compensation expense related to awards to employees and directors with service-based vesting conditions is recognized on a straight-line basis based on the grant date fair value over the associated service period of the award, which is generally the vesting term. Compensation expense related to awards to non-employees with service-based vesting conditions is recognized based on the then-current fair value at each financial reporting date prior to the measurement date over the associated service period of the award, which is generally the vesting term. Compensation expense related to awards to employees with performance-based vesting conditions is recognized based on the grant date fair value over the requisite service period to the extent achievement of the performance condition is probable.

The Company estimates the fair value of its option awards to employees and directors using the Black-Scholes option pricing model, which requires the input of subjective assumptions, including (i) the expected stock price volatility, (ii) the calculation of the expected term of the award, (iii) the risk-free interest rate and (iv) expected dividends. Due to the lack of substantial Company-specific historical and implied volatility data of its common stock, the Company has based its estimate of expected volatility on the historical volatility of a group of similar companies that are publicly traded. When selecting these public companies on which it has based its expected stock price volatility, the Company selected companies with comparable characteristics to it, including enterprise value, risk profiles, position within the industry and with historical share price information sufficient to meet the expected term of the stock-based awards. The Company computes historical volatility data using the daily closing prices for the selected companies' shares during the equivalent period of the calculated expected term of the stock-based awards. The Company will continue to apply this process until a sufficient amount of historical information regarding the volatility of its own stock price becomes available. The Company has estimated the expected term of its employee stock options using the "simplified" method, whereby, the expected term equals the arithmetic average of the vesting term and the original contractual term of the option due to its lack of sufficient historical data. The risk-free interest rates for periods within the expected term of the option are based on the U.S. Treasury securities with a maturity date commensurate with the expected term of the associated award. The Company has never paid, and does not expect to pay, dividends in the foreseeable future. The Company accounts for forfeitures when they occur.

Consistent with the guidance in ASC Topic 505-50, *Equity-Based Payments to Non-Employees*, the fair value of each non-employee stock option and restricted stock award is estimated at the date of grant using the Black-Scholes option pricing model with assumptions generally consistent with those used for employee stock options, with the exception of expected term, which is over the contractual life.

(n) Net loss per common share

Basic and diluted net loss per common share is determined by dividing net loss by the weighted average number of common shares outstanding during the period. For all periods presented, unvested restricted shares and common stock options have been excluded from the calculation because their effect would be anti-dilutive. Therefore, the weighted average shares outstanding used to calculate both basic and diluted loss per share are the same.

The following potentially dilutive securities have been excluded from the computations of diluted weighted average shares outstanding for the years ended December 31, 2016, 2017 and 2018 as they would be anti-dilutive:

	December 31,		
	2016	**2017**	**2018**
Unvested restricted common shares	251,809	798,501	942,776
Options issued and outstanding	4,181,993	3,522,874	3,487,376

Amounts in the table above reflect the common stock equivalents of the noted instruments.

(o) Deferred rent

Rent expense, including rent holidays and scheduled rent increases, is recorded on a straight-line basis over the term of the lease commencing on the date the Company takes possession of the leased property. Tenant improvement allowances from the lessor are included in the accompanying consolidated balance sheet as deferred rent and are amortized as a reduction of rent

Spark Therapeutics, Inc.
Notes to consolidated financial statements

expense over the term of the lease from the possession date. Deferred rent as of December 31, 2017 and 2018 represents the net excess of rent expense over the actual cash paid for rent and the tenant improvement allowances received.

(p) Other comprehensive loss

The Company follows the provisions of ASC Topic 220, *Comprehensive Income*, which establishes standards for the reporting and display of comprehensive income and its components. Comprehensive income (loss) is defined to include all changes in equity during a period except those resulting from investments by owners and distributions to owners. Comprehensive income (loss) includes gains and losses related to changes in the fair value of available-for-sale securities, changes in the fair value of an interest rate swap and foreign currency translation. The accumulated balances related to each component of other comprehensive income (loss) are summarized as follows (in thousands):

	Net unrealized (loss) gain on available-for-sale securities	Unrealized loss on interest rate swap	Foreign currency translation adjustments	Accumulated other comprehensive loss
Balance as of December 31, 2017	$ (5,964)	$ —	$ 50	$ (5,914)
Reclassification of unrealized loss on equity investment to accumulated deficit	5,002	—	—	5,002
Current period other comprehensive income (loss)	586	(641)	(83)	(138)
Balance as of December 31, 2018	$ (376)	$ (641)	$ (33)	$ (1,050)

(q) Recent accounting pronouncements

In February 2016, the Financial Accounting Standards Board (FASB) issued Accounting Standards Update (ASU) 2016-02, *Leases*. ASU 2016-02 requires lessees to apply a two-method approach, classifying leases as either finance or operating leases based on the principle of whether or not the lease is effectively a financed purchase. This classification will determine whether lease expense is recognized based on an effective interest method or on a straight line basis over the term of the lease, respectively. Lessees are also required to record a right-of-use (ROU) asset and a lease liability for all leases with a term greater than 12 months. Leases with a term of 12 months or less will be accounted for similar to existing guidance for operating leases. ASU 2016-02 is effective for interim and annual periods beginning after December 15, 2018. The Company has elected to adopt this standard using the effective date method using a modified retrospective transition approach. The Company expects the adoption of the standard to have a material impact on its consolidated balance sheet, which will result in the removal of the built to suit asset and liability recorded as of December 31, 2018, and the recognition of ROU assets and lease liabilities of approximately $40.0 million to $50.0 million at January 1, 2019.

In May 2014, the FASB issued a new standard, ASC 606, regarding the accounting for, and disclosures of, revenue recognition, with an effective date for annual and interim periods beginning after December 15, 2017. ASC 606 provides a single comprehensive model for accounting for revenue from contracts with customers. The model requires that revenue recognized reflect the actual consideration to which the entity expects to be entitled in exchange for the goods or services defined in the contract, including in situations with multiple performance obligations. The Company adopted ASC 606 using the modified retrospective method and the adoption had no cumulative adjustment to its consolidated financial statements as it relates to the Pfizer Inc. (Pfizer) collaboration agreement discussed in Note 16. For the year ended December 31, 2018, there was no impact from the adoption of ASC 606 that resulted in a different revenue recognition amount than under the prior revenue recognition guidance in effect during 2017.

In January 2016, the FASB issued ASU 2016-01, *Financial Instruments-Overall: Recognition and Measurement of Financial Assets and Financial Liabilities*. ASU 2016-01 changes accounting for equity investments, financial liabilities under the fair value option, and presentation and disclosure requirements for financial instruments. ASU 2016-01 does not apply to equity investments in consolidated subsidiaries or those accounted for under the equity

method of accounting. In addition, the FASB clarified guidance related to the valuation allowance assessment when recognizing deferred tax assets resulting from unrealized losses on available-for-sale debt securities. Equity investments with readily determinable fair values will be measured at fair value with changes in fair value recognized in net income. Companies have the option to either measure equity investments without readily determinable fair values at fair value or at cost, adjusted for changes in observable prices, minus impairment. Changes in measurement under either alternative will be recognized in net income. Companies that elect the fair value option for financial liabilities must recognize changes in fair value related to instrument-specific credit risk in other comprehensive

Spark Therapeutics, Inc.
Notes to consolidated financial statements

income. Companies must assess valuation allowances for deferred tax assets related to available-for-sale debt securities in combination with their other deferred tax assets. The Company adopted this guidance effective January 1, 2018, resulting in a reclassification of $5.0 million from accumulated other comprehensive loss to accumulated deficit related to the unrecognized loss on the Company's investment in Selecta.

In August 2017, the FASB issued ASU 2017-12, *Derivatives and Hedging: Targeted Improvements to Accounting for Hedging Activities*, which improves the financial reporting of hedging relationships to better portray the economic results of an entity's risk management activities in its financial statements and make certain targeted improvements to simplify the application of the hedge accounting guidance in current U.S. GAAP. The amendments in this update better align an entity's risk management activities and financial reporting for hedging relationships through changes to both the designation and measurement guidance for qualifying hedging relationships and the presentation of hedge results. The effective date for the standard is for fiscal years beginning after December 15, 2018. The Company elected to early adopt this ASU in the third quarter of 2018. The adoption of this guidance did not have a material impact on the Company’s consolidated financial statements. See Note 11 for a discussion of the Company’s derivatives.

(4) Marketable securities

The following table summarizes the available-for-sale securities held as of December 31, 2017 and 2018 (in thousands):

Description	Amortized cost	Unrealized gains	Unrealized losses	Fair value
December 31, 2017				
U.S. government agency	$ 222,180	$ —	$ (641)	$ 221,539
Corporate securities	$ 227,238	$ —	$ (5,323)	$ 221,915
December 31, 2018				
U.S. government agency	$ 223,553	$ 54	$ (123)	$ 223,484
Corporate securities	$ 239,940	$ 34	$ (10,421)	$ 229,553

No available-for-sale securities held as of December 31, 2018, had remaining maturities greater than two years.

(5) Fair value of financial instruments

The Company follows FASB accounting guidance on fair value measurements for financial assets and liabilities measured on a recurring basis. The guidance requires fair value measurements to maximize the use of “observable inputs.” The three-level hierarchy of inputs to measure fair value are as follows:

- Level 1: Unadjusted quoted prices in active markets that are accessible at the measurement date for identical, unrestricted assets or liabilities
- Level 2: Significant other observable inputs other than Level 1 prices such as quoted prices in markets that are not active, or inputs that are observable, either directly or indirectly, for substantially the full term of the asset or liability
- Level 3: Prices or valuation techniques that require inputs that are both significant to the fair value measurement and unobservable (i.e., supported by little or no market activity)

F-15

Spark Therapeutics, Inc.
Notes to consolidated financial statements

The Company has classified assets and liabilities measured at fair value on a recurring basis as follows (in thousands):

	Fair value measurements at reporting date using Quoted prices in active markets for identical assets (Level 1)	Significant other observable inputs (Level 2)	Significant unobservable inputs (Level 3)
As of December 31, 2017:			
Assets:			
Money market funds (included in cash and cash equivalents)	$90,348	—	—
Corporate securities (included in cash and cash equivalents)	$5,548	—	—
Marketable securities - U.S. government agencies	$221,539	—	—
Marketable securities - corporate securities	$220,020	$ 1,895	—
As of December 31, 2018:			
Assets:			
Money market funds (included in cash and cash equivalents)	$94,216	—	—
Certificates of deposit - restricted cash	$53,000	—	—
Marketable securities - U.S. government agencies	$223,484	—	—
Marketable securities - corporate securities	$229,553	—	—

(6) Inventory

Inventory consists of the following (in thousands):

	December 31, 2018
Raw materials	$ 3,843
Work in process	19,843
Finished goods	1,951
	$ 25,637

(7) Sale of priority review voucher

In May 2018, the Company sold the rare pediatric disease priority review voucher (PRV) it received from FDA in connection with the United States approval of LUXTURNA to Jazz Pharmaceuticals Ireland Limited for consideration of $110.0 million. The proceeds from the sale of the PRV were recognized as a gain on the sale of an intangible asset, within other income on the consolidated statements of operations and comprehensive income (loss), as the PRV did not have a carrying value on the Company’s consolidated balance sheet at the time of sale.

(8) Business acquisition of Genable and impairment of acquired in-process research and development

On March 7, 2016, the Company acquired Genable Technologies, Ltd. (Genable), an Ireland-based private gene therapy company with which the Company had collaborated since 2014 in the development of Genable's therapeutic program targeting a genetic inherited retinal disease (IRD). With the acquisition, the Company acquired RhoNova™, a potential gene therapy targeting rhodopsin-linked autosomal dominant retinitis pigmentosa (RHO-adRP), an IRD that

routinely leads to visual impairment and in the most severe cases to blindness. The consideration paid by the Company to Genable shareholders consisted of $6.1 million in cash and 265,000 shares of the Company's common stock with a fair value of $9.2 million, for total consideration of $15.3 million. In connection with the acquistion, a receivable due from Genable also was settled on the date of acquisition for $0.5 million. The Company incurred acquisition-related costs of approximately $0.3 million, which are included

Spark Therapeutics, Inc.
Notes to consolidated financial statements

in selling, general and administrative expenses in the consolidated statement of operations for the year ended December 31, 2016.

The Company accounted for the acquisition as a business combination under the acquisition method of accounting. The Company allocated the purchase price for the purchase of Genable based upon the estimated fair value of net assets acquired and liabilities assumed at the date of acquisition.

Recognition and measurement of assets acquired and liabilities assumed

The following table summarizes the fair values of the tangible and intangible assets acquired and liabilities assumed at the acquisition date (in thousands):

Cash acquired	$196
Other current assets	103
Acquired in-process research and development	15,490
Goodwill	1,160
Total assets assumed	16,949
Other non-current liabilities	255
Deferred tax liability	1,000
Total liabilities assumed	1,255
Total allocation of purchase price	$15,694

Acquired in-process research and development and related impairment

The Company's allocation of purchase price to acquired in-process research and development (IPR&D) was $15.5 million. The estimated fair value of the IPR&D was determined using the "income approach," which is a valuation technique that provides an estimate of the fair value of an asset based on market participant expectations of the cash flows an asset would generate over its remaining useful life. Some of the more significant assumptions inherent in the development of those asset valuations include the estimated net cash flows for each year for the asset or product (including net revenues, cost of sales, research and development costs, selling and marketing costs and working capital/asset contributory asset charges), the appropriate discount rate to select in order to measure the risk inherent in each future cash flow stream, the assessment of the asset's life cycle, the potential regulatory and commercial success risks, competitive trends impacting the asset cash flow stream as well as other factors.

During the year ended December 31, 2017, the Company determined that it would no longer pursue product candidates utilizing the technology acquired from Genable in March 2016 and, accordingly, recorded an impairment charge of $15.7 million within its consolidated statement of operations. Additionally, the Company recognized an income tax benefit of $1.0 million related to the reversal of the deferred tax liability associated with the IPR&D during the year ended December 31, 2017.

Goodwill impairment

Goodwill represents the excess of purchase price over the fair value of net assets acquired by the Company. Goodwill is not amortized, but assessed for impairment on an annual basis or more frequently if impairment indicators exist. The Company operates as one reporting unit.

The Company has the option to perform a qualitative assessment of goodwill prior to completing the two-step method described below to determine whether or not it is more likely than not that the fair value of its reporting units is less than its carrying amount, including goodwill and other intangible assets. If the Company concludes that this is the case, it must perform the two-step process.

The first step compares a reporting unit's fair value to its carrying amount to identify potential goodwill impairment. If the carrying amount of a reporting unit exceeds the reporting unit's fair value, the second step of the impairment test must be completed to measure the amount of the reporting unit's goodwill impairment loss, if any. Step two requires an assignment of the reporting unit's fair value to the reporting unit's assets and liabilities to determine the implied fair

value of the reporting unit's goodwill. The implied fair value of the reporting unit's goodwill is then compared with the carrying amount of the reporting unit's goodwill to determine the goodwill impairment loss to be recognized, if any.

Spark Therapeutics, Inc.
Notes to consolidated financial statements

The Company performs its annual goodwill impairment test as of October 1st. The Company performed a qualitative assessment and determined that there was no impairment to goodwill for the years ended December 31, 2016, 2017 and 2018.

(9) Property and equipment, net

Property and equipment consist of the following (in thousands):

	December 31,	
	2017	**2018**
Laboratory equipment	$6,381	$8,272
Computer and software	1,325	2,773
Furniture and fixtures	1,770	2,564
Office equipment	726	1,394
Leasehold improvements	23,653	54,541
One Drexel Plaza (built-to-suit)	34,993	34,789
Construction in progress	3,187	7,869
Property and equipment, gross	72,035	112,202
Less accumulated depreciation and amortization	(10,322)	(16,204)
Property and equipment, net	$61,713	$95,998

Depreciation and amortization expense was $3.6 million, $4.9 million and $6.9 million for the years ended December 31, 2016, 2017 and 2018, respectively.

(10) Accrued expenses

Accrued expenses consist of the following (in thousands):

	December 31,	
	2017	**2018**
Compensation and benefits	$15,012	$15,575
Consulting and professional fees	4,846	13,904
Research and development	2,809	2,706
Other	2,030	2,605
	$24,697	$34,790

(11) Debt

The Company's debt consists of the following (in thousands):

	December 31,	
	2017	**2018**
Term loan outstanding	$—	$50,000
MELF loan outstanding	1,224	912
Less: current portion of long-term debt	(312)	(4,822)
Total long-term debt due after one year	$912	$46,090

In July 2018, the Company entered into a credit agreement with Wells Fargo Bank, National Association (Wells Fargo) as lender (the Credit Agreement), pursuant to which Wells Fargo extended a $50.0 million term loan to the Company, which bears interest at one-month LIBOR plus 0.65%, which rate is converted to a fixed rate per annum of 3.463% under the swap agreement discussed below. The term loan was fully drawn on the date of the Credit Agreement and matures on July 3, 2023 (Maturity Date). Through June 2019, the Company will only be obligated to

make monthly interest payments with respect to

Spark Therapeutics, Inc.
Notes to consolidated financial statements

the term loan. Thereafter, the term loan will amortize in equal monthly installments through the maturity date. For the year ended December 31, 2018, the Company recorded interest expense of $0.7 million related to the Credit Agreement.

In order to manage the interest risk associated with the term loan, the Company entered into an interest rate swap with Wells Fargo on an initial notional amount of $50.0 million. Under this interest rate swap agreement, which expires on July 3, 2023, the Company receives a floating rate based on 1-month LIBOR plus 0.65% and pays a fixed rate of 3.463%. The Company designated this interest rate swap as a cash flow hedge of the forecasted interest payments related to the debt issuance. To maintain this rate, the Company entered into a cash collateral agreement with Wells Fargo that requires the Company to maintain a restricted cash balance equal to at least the principal balance of the term loan.

At December 31, 2018, the fair value of the derivative liability was $0.6 million, of which $0.1 million was recognized within other current liabilities and $0.5 million was recognized within other long-term liabilities. The effective portion of the swap is reported as a component of accumulated other comprehensive loss. There was no hedge ineffectiveness as of December 31, 2018. Changes in the fair value are reclassified from accumulated other comprehensive loss into operations in the same period that the hedged item affects earnings. During the year ended December 31, 2018, the Company reclassified $0.2 million from accumulated other comprehensive loss into interest expense related to the effective portion of the swap. Over the next 12 months, $0.6 million of the effective portion of the interest rate swap is expected to be reclassified from accumulated other comprehensive loss into interest expense. If, at any time, the interest rate swap is determined to be ineffective, in whole or in part, due to changes in the interest rate swap or underlying debt agreements, the fair value of the portion of the interest rate swap determined to be ineffective will be recognized as a gain or loss in the statement of operations and comprehensive income (loss) for the applicable period.

In August 2016, the Company executed an agreement with the Commonwealth of Pennsylvania to fund machinery and equipment and other assets purchased (MELF Loan) in the amount of $1.6 million. Borrowings under the MELF Loan are secured by equipment, as defined in the loan agreement. Under the terms of the MELF Loan, the Company has a five-year period of monthly payments of $29 thousand of principal and interest at an annual interest rate of 3.25%. For the years ended December 31, 2016, 2017 and 2018, the Company recorded interest expense of $15 thousand, $48 thousand and $34 thousand, respectively, related to the MELF Loan.

(12) Stockholders' equity

The Company's certificate of incorporation and bylaws contain the rights, preferences and privileges of the Company's stockholders and their respective shares. The Company has authorized 150,000,000 shares of common stock and 5,000,000 shares of preferred stock.

In 2013 and 2014, the Company issued restricted stock to various employees, directors and consultants of the Company. The vesting terms of the restricted stock issued varied, but primarily, shares vested 25% on the first anniversary of the vesting commencement date and then quarterly over three years, with accelerated vesting in the event of a change in control, as defined. Any unvested shares are forfeited in the event that the individual ceases to provide services to the Company.

Additionally, in 2014, 200,000 restricted shares of common stock were issued to The Trustees of the University of Pennsylvania (Penn) in connection with a license agreement, of which 175,000 shares have vested. The remaining shares were canceled during the year ended December 31, 2018.

For the year ended December 31, 2016, the Company recorded compensation expense of $0.1 million and $1.3 million in selling, general and administrative expense and research and development expense, respectively, related to the restricted shares. For the year ended December 31, 2017, the Company recorded compensation expense of $34 thousand and $4.4 million in selling, general and administrative expense and research and development expense,

respectively, related to the restricted shares. For the year ended December 31, 2018, the Company recorded an immaterial amount of compensation expense in selling, general and administrative expense and $2.2 million of expense in research and development expense related to the restricted shares.

Spark Therapeutics, Inc.
Notes to consolidated financial statements

The following table summarizes restricted stock activity for the instruments discussed above:

	Number of shares	Weighted-average grant date fair value
Nonvested shares at December 31, 2016	174,876	$ 5.78
Shares canceled	(3,107)	$ 1.15
Shares vested	(70,935)	$ 3.60
Nonvested shares at December 31, 2017	100,834	$ 7.45
Shares canceled	(25,000)	$ 7.50
Shares vested	(75,834)	$ 7.44
Nonvested shares at December 31, 2018	—	

On June 20, 2016, the Company completed a follow-on public offering, having sold 3,025,000 shares of common stock at an offering price of $45.00 per share, for aggregate gross proceeds of $136.1 million. The Company received net proceeds from the public offering of $127.6 million, after deducting underwriting discounts and commissions and other offering costs.
On August 9, 2017, the Company completed a follow-on public offering, having sold 5,296,053 shares of common stock at an offering price of $76.00 per share, for aggregate gross proceeds of $402.5 million. The Company received net proceeds from the public offering of $379.9 million, after deducting underwriting discounts and commissions and other offering costs.

(13) Stock incentive plans
The Company's 2015 Stock Incentive Plan (the 2015 Plan) provides for the grant of incentive stock options, nonstatutory stock options, stock appreciation rights, restricted stock awards, restricted stock units and other stock-based awards to employees, officers, directors, consultants and advisors. In January 2018, the number of shares of common stock authorized for issuance under the 2015 Plan automatically increased, pursuant to the terms of the 2015 Plan, by 1,485,322 shares. As of December 31, 2018, 1,422,190 shares were available for future grants under the 2015 Plan.
In January 2018, the number of shares of common stock authorized for issuance under the 2015 Employee Stock Purchase Plan (ESPP) automatically increased, pursuant to the terms of the 2015 ESPP, by 371,330 shares. The 2015 ESPP provides participating employees with the opportunity to purchase an aggregate of 1,120,188 shares of common stock as of December 31, 2018.

Stock-based compensation expense
Stock-based compensation expense by award type was as follows (in thousands):

	Year ended December 31,		
	2016	2017	2018
Stock options	$22,377	$28,001	$29,674
Restricted stock	632	8,452	16,141
Employee stock purchase plan	178	438	610
	$23,187	$36,891	$46,425

Of the $46.4 million of stock-based compensation expense incurred during the year ended December 31, 2018, $18.0 million is classified as research and development expense and $28.4 million is classified as selling, general and administrative expense in the consolidated statement of operations and comprehensive income (loss). Of the $36.9

million of stock-based compensation expense incurred during the year ended December 31, 2017, $15.1 million is classified as research and development expense and $21.8 million is classified as selling, general and administrative expense in the consolidated statement of operations and comprehensive income (loss). Of the $23.2 million of stock-based compensation expense incurred during the year ended December 31, 2016, $9.6 million is classified as research and development expense and $13.6 million is classified as selling, general and administrative expense in the consolidated statement of operations and comprehensive income (loss).

Spark Therapeutics, Inc.
Notes to consolidated financial statements

Stock options

The following table summarizes stock option activity:

	Number of shares	Weighted-average exercise price	Aggregate intrinsic value(a)
Outstanding at December 31, 2016	4,181,993	$ 33.25	
Granted	701,300	$ 56.78	
Exercised	(953,253)	$ 21.75	
Forfeited	(407,166)	$ 41.30	
Outstanding at December 31, 2017	3,522,874	$ 40.11	
Granted	671,500	$ 52.02	
Exercised	(453,905)	$ 33.34	
Forfeited	(253,093)	$ 52.32	
Outstanding at December 31, 2018	3,487,376	$ 42.40	
Vested at December 31, 2018	1,934,833	$ 35.17	$25,798,486
Vested at December 31, 2018 and expected to vest	3,315,852	$ 41.92	$26,194,775

(a) The aggregate intrinsic value is calculated as the difference between the exercise price of the underlying options and the fair value of the common stock that were in the money at December 31, 2018.

The weighted average remaining contractual term of options outstanding as of December 31, 2018 is 7.2 years. The weighted-average remaining contractual term of options exercisable as of December 31, 2018 is 6.4 years.

At December 31, 2018, there was $42.2 million of unrecognized compensation expense related to stock options, which is expected to be recognized over a weighted-average period of 2.2 years.

The intrinsic value of options exercised during the years ended December 31, 2017 and 2018 was $45.9 million and $16.6 million, respectively.

The weighted-average grant date fair value of the options granted in 2016, 2017 and 2018 was $28.56, $39.27 and $35.14 per share, respectively, using the Black-Scholes option-pricing model with the following weighted-average assumptions:

	Years Ended December 31,		
	2016	2017	2018
Expected volatility	75.2%	78.1%	75.7%
Risk-free interest rate	1.71%	2.06%	2.50%
Expected term (in years)	5.95	6.10	6.21
Expected dividend yield	0.0 %	0.0 %	0.0 %

Spark Therapeutics, Inc.
Notes to consolidated financial statements

Restricted stock
The following table summarizes restricted common stock activity:

	Number of shares	Weighted-average grant date fair value
Nonvested shares at December 31, 2016	76,933	$ 49.90
Shares granted	713,400	$ 63.34
Shares canceled	(55,457)	$ 48.93
Shares vested	(37,209)	$ 55.77
Nonvested shares at December 31, 2017	697,667	$ 63.40
Shares granted	553,300	$ 54.29
Shares canceled	(123,656)	$ 60.75
Shares vested	(184,535)	$ 61.87
Nonvested shares at December 31, 2018	942,776	$ 58.71

At December 31, 2018, there was $43.1 million of unrecognized compensation expense related to the restricted common stock, which is expected to be recognized over a weighted average period of 2.8 years.

ESPP stock activity:
For the year ended December 31, 2017, 11,804 shares were issued under the 2015 ESPP. For the year ended December 31, 2018, 30,814 shares were issued under the 2015 ESPP.
At December 31, 2018, there was $0.3 million in unrecognized compensation expense related to the 2015 ESPP.

(14) Commitments and contingencies
(a) Leases

In March 2014, the Company entered into an operating lease for laboratory and office space at its corporate headquarters in Philadelphia, Pennsylvania, through October 2025. Under this lease, the Company received $8.0 million of tenant improvement allowances during 2014. In November 2015, the Company entered into a sublease agreement for approximately 14,000 square feet of additional office space at its corporate headquarters. The sublease terminated on November 30, 2018. In February 2016, the Company leased 6,500 square feet of additional office space in Philadelphia under a lease that expires in June 2021.

In November 2016, the Company entered into a lease agreement for approximately 49,000 square feet of office space in Philadelphia that will terminate on March 31, 2027. Under this lease, the Company received $1.6 million of tenant improvement allowances during 2017. In January 2017, the Company amended its lease for office space in Philadelphia to lease an additional 24,800 square feet that commenced on January 1, 2018, and will terminate on December 31, 2028. In November 2017, the Company amended this lease to accelerate the termination date of approximately 50,000 square feet of office space, with such termination to occur, at the latest, in December 2022. The Company recorded an expense of $6.9 million associated with the change in termination date in 2017. As of December 31, 2018, $3.5 million is recorded as long-term other liabilities and $1.8 million is recorded as current other liabilities on the accompanying consolidated balance sheet related to the termination expense.

The following table reconciles the termination cost discussed above (in thousands):

	Balance as of December 31, 2017	Recognized during the year	Balance as of December 31, 2018

Contract termination liability	$6,827	$1,557	$5,270

Spark Therapeutics, Inc.
Notes to consolidated financial statements

In November 2017, the Company entered into a lease for the new research facility at One Drexel Plaza in Philadelphia, Pennsylvania for approximately 108,000 square feet through June 2033. Under this lease, the Company received $3.9 million of tenant improvement allowances during 2018.

Based on the terms of the lease agreement for One Drexel Plaza, the Company had construction period risks during the construction period and the Company was deemed the owner of the building (for accounting purposes only) during the construction period. Accordingly, the Company recorded an asset of $35.0 million as of December 31, 2017, representing the Company's leased portion of the building, and recorded a corresponding liability. Upon completion of leasehold improvement construction, the Company may not meet the sale-leaseback criteria for de-recognition of the building asset and liability. Therefore, the lease may be accounted for as a financing obligation. The asset will be depreciated over the expected duration of the lease of 15.5 years, and rental payments will be treated as principal and interest payments on the lease financing obligation liability. The underlying accounting for this transaction has no impact on cash flows associated with the underlying lease or construction in process.

At December 31, 2017 and 2018, the lease financing obligation balance was $35.0 million and $34.5 million, respectively, and was recorded as a long-term liability within other liabilities on the consolidated balance sheets. The remaining future minimum payments under the lease financing obligation as of December 31, 2018 are included in the table below.

In May 2018, the Company entered into a lease agreement for approximately 14,000 square feet of office space in Philadelphia that will terminate in April 2020. Under this lease, the Company received $0.1 million of tenant improvement allowances during 2018.

Rent expense under these leases was $1.9 million, $10.5 million and $3.9 million for the years ended December 31, 2016, 2017 and 2018, respectively.

Future minimum lease payments under these leases are as follows (in thousands):

Year Ending December 31,	
2019	$8,102
2020	11,044
2021	10,073
2022	10,156
2023	9,228
2024 and thereafter	78,079
	$126,682

(b) Manufacturing agreement

In August 2018, the Company entered into a Dedicated Manufacturing and Commercial Supply Agreement (the Brammer Agreement) with Brammer Bio MA, LLC (Brammer), pursuant to which Brammer has agreed to manufacture and supply certain products for the Company for clinical trial and commercial purposes. The term of the agreement continues until March 2026 and shall automatically renew for successive three (3) year terms unless the Company notifies Brammer of its intention not to renew no less than two (2) years prior to the expiration of the original term. During the term of the agreement, the Company will have access to a dedicated, specified portion of the manufacturing capacity in Brammer's manufacturing facility located in Cambridge, Massachusetts, as well as non-dedicated capacity at Brammer's facilities for manufacturing and other supply-related activities. Under the Brammer Agreement, the Company made an upfront payment of $4.0 million to Brammer upon execution of the

agreement, which is included as a prepaid asset on the consolidated balance sheet and will be credited towards future capacity access amounts owed under the Brammer Agreement. The Company is obligated to pay yearly capacity access fees and is required to purchase a minimum dollar amount of manufactured batches per year.

(c) License agreements

See Note 15 for a discussion of the Children's Hospital of Philadelphia (CHOP) license agreement.

In October 2013, the Company entered into a patent license agreement with Penn, as amended, for certain intellectual property licenses to be provided by Penn to the Company in the fields of research, development, manufacture and commercialization. The license agreement requires the Company to reimburse Penn for the patent costs related to the underlying licensed rights.

Spark Therapeutics, Inc.
Notes to consolidated financial statements

The Company is obligated to make payments to Penn upon the occurrence of first commercial sale for certain licensed products in both the United States and Europe. The Company must pay a low-single-digit royalty based on net sales of licensed products by territory, which royalties will be reduced if the Company is required to license patents or intellectual property from third parties.

In December 2014, the Company entered into a license agreement with Penn for certain intellectual property licenses. The Company issued to Penn 200,000 shares of restricted common stock (Note 12), which were subject to performance-based vesting conditions, in connection with the agreement and is obligated to make milestone payments upon the achievement of certain regulatory milestones up to $5.5 million in the aggregate. Additionally, the Company is obligated to pay Penn single-digit-royalties based on its net sales of licensed products by territory.

In October 2013, the Company entered into a license agreement with the University of Iowa Research Foundation (UIRF) for certain intellectual property licenses. The license agreement requires the Company to reimburse UIRF for the patent costs related to the underlying licensed rights. The Company is obligated to make payments to UIRF upon the occurrence of various development and commercialization milestones. The Company must pay a low-single-digit royalty to UIRF based on net sales of licensed products by territory.

(15) Related-party transactions

As of December 31, 2018, CHOP was considered a significant equity holder. In October 2013, the Company entered into technology and license agreements with CHOP for certain commercialization licenses to be provided to the Company in order to develop services, methods and marketable products for commercialization. The license agreement requires the Company to reimburse CHOP for the patent costs related to the underlying licensed rights incurred after the effective date. For the years ended December 31, 2016, 2017 and 2018, the Company recorded $0.9 million, $0.8 million and $1.2 million, respectively, of selling, general and administrative expense related to the reimbursement of such patent costs in the accompanying consolidated statements of operations and comprehensive income (loss).

In 2013, the Company entered into a number of services agreements with CHOP. The Master Research Services Agreement provides for certain research, development and manufacturing services to be provided to the Company by CHOP. A separate Services Agreement provides for clinical, technical and administrative services to be provided by CHOP to the Company. For the years ended December 31, 2016, 2017 and 2018, the Company recorded $7.4 million, $6.1 million and $5.7 million, respectively, as research and development expense.

As of December 31, 2017, $0.3 million and $1.4 million were recorded in accrued expenses and accounts payable, respectively, as amounts due to CHOP. As of December 31, 2018, $0.7 million and $0.5 million were recorded in accrued expenses and accounts payable, respectively, as amounts due to CHOP.

(16) Collaboration and license agreements

(a) Pfizer

In December 2014, the Company entered into a global collaboration agreement with Pfizer for the development and commercialization of SPK-FIX product candidates for the treatment of hemophilia B. Under the agreement, the Company granted Pfizer an exclusive worldwide license to any factor IX gene therapy that it develops, manufactures or commercializes prior to December 31, 2024. The Company is primarily responsible for conducting all research and development activities through completion of Phase 1/2 clinical trials of hemophilia B product candidates. Pfizer and the Company will share development costs incurred under an agreed product development plan for each product candidate with the Company’s share of development costs under the agreement limited to $10.6 million. Following the completion of Phase 1/2 clinical trials, Pfizer will be primarily responsible for development, manufacture, regulatory approval and commercialization, including all costs associated therewith. In connection with this agreement, the Company received a $20.0 million upfront payment for the license in December 2014. As there was no stand-alone value for the license, the Company recognized revenue through the estimated completion date of Phase 1/2 clinical trials. In November 2017, the Company amended its global collaboration agreement with Pfizer. Under the terms of this amendment, the Company received $15.0 million in payments upfront, and an additional $10.0 million upon

completion of certain transition activities. The $25.0 million of consideration was recognized as revenue over the estimated performance period associated with the global collaboration agreement.

The Company is eligible to receive up to an additional $230.0 million in aggregate milestone payments, $110.0 million of which relate to potential development, regulatory and commercial milestones for the first product candidate to achieve each milestone and $120.0 million of which relate to potential regulatory milestones for additional product candidates. In addition, the Company is entitled to receive royalties calculated as a low-teen percentage of net sales of licensed products. The royalties may be subject to certain reductions, including for a specified portion of royalty payments that Pfizer may become required to

pay under any third-party license agreements, subject to a minimum royalty. Under the agreement, the Company remains solely responsible for the payment of license payments payable by the Company under specified license agreements.

The agreement will expire on a country-by-country basis upon the latest of: (i) the expiration of the last-to-expire valid claim, as defined in the agreement, in licensed patent rights covering a licensed product; (ii) the expiration of the last-to-expire regulatory exclusivity granted with respect to a licensed product; or (iii) 15 years after the first commercial sale of the last licensed product to be launched, in each case, in the applicable country. Pfizer may terminate the agreement on a licensed product-by-licensed product and country-by-country basis, or in its entirety, for any or no reason subject to notice requirements.

In February 2018, the Company entered into a supply agreement with Pfizer for production in 2018, of one batch of drug substance expected to be used for Phase 3 development. The Company received $7.0 million upfront and received $7.0 million upon delivery in July 2018. The $14.0 million of consideration was recognized as contract revenue as the batch of the drug substance was completed.

During the years ended December 31, 2016, 2017 and 2018, the Company recognized $20.2 million, $12.1 million and $36.0 million of contract revenue, respectively, related to the Company's agreements with Pfizer. During the years ended December 31, 2016, 2017 and 2018, the Company recorded $2.4 million, $2.9 million and $3.0 million, respectively, as a reduction to research and development expenses for the reimbursement of costs from Pfizer. In July 2018, Pfizer announced the initiation of a Phase 3 program following the Company's transfer of responsibility for the hemophilia B gene therapy program to Pfizer.

(b) Novartis

In January 2018, the Company entered into a licensing and commercialization agreement (Novartis License Agreement) with Novartis Pharma AG (Novartis) to develop and commercialize voretigene neparvovec (also known as LUXTURNA) outside the United States. Under the terms of the Novartis License Agreement, the Company has granted Novartis an exclusive right and license, with the right to grant certain sublicenses, under the Company’s intellectual property reasonably necessary or useful for the development or commercialization of LUXTURNA for the treatment, prevention, cure or control of RPE65-mediated IRD in humans outside the United States. Under the terms of the Novartis License Agreement, the Company received a non-refundable, one-time payment of $105.0 million in the first quarter of 2018, and is eligible to receive up to an additional $65.0 million in milestone payments. The Company also is entitled to receive royalty payments at a percentage of net sales on a royalty-region by royalty-region basis, subject to reduction and extension in certain circumstances.

In conjunction with the Novartis License Agreement, the Company and Novartis also entered into a Supply Agreement, under which the Company has agreed to supply all of the commercial supply of voretigene neparvovec required by Novartis, subject to certain conditions. The Supply Agreement continues until the expiration or early termination of the Novartis License Agreement. In addition, either party may terminate the Supply Agreement upon the other party’s uncured material breach of the Supply Agreement, insolvency or bankruptcy. The Company evaluated whether or not the performance obligations granted under the License and Supply Agreements were distinct and concluded that they were not distinct as Novartis could not benefit from the Novartis License Agreement without the services under the Supply Agreement. As such, the performance obligations granted under the Novartis License Agreement and Supply Agreement are combined to constitute a single performance obligation and the Company accounts for them as a single contract.

During the fourth quarter of 2018, and in conjunction with the European Commission granting marketing authorization for LUXTURNA, the Company earned an additional $25.0 million milestone payment and recorded an additional $30.0 million of variable consideration that was no longer constrained which, along with the $105.0 million upfront payment, is included as deferred revenue on the accompanying consolidated balance sheet as of December 31, 2018. The Company allocated $160.0 million in license fees and milestone payments that were not constrained to the single performance obligation in the combined contracts. The Company expects to recognize the $160.0 million and variable amounts under the Supply Agreement over time using an outputs method based on vials supplied to Novartis. The Company expects to begin manufacturing product for Novartis in 2019 and expects to continue to do so

throughout the life of the contract. At December 31, 2018, the remaining $10.0 million in milestone payments under the Novartis License Agreement remains constrained, due to additional regulatory approvals, and will not begin to be recognized until such amount becomes unconstrained.

In determining the transaction price, the Company analyzed the variable consideration and whether or not such variable consideration was constrained. The Company will reassess this variable consideration at each reporting period and adjust the transaction price, if necessary. The total vials that the Company expects to manufacture for Novartis over the life of the Supply Agreement will be a significant judgment that will be relied upon when using the point in time method to recognize revenue once the Company begins to manufacture product for Novartis.

(c) Selecta

Spark Therapeutics, Inc.
Notes to consolidated financial statements

In December 2016, the Company entered into a License and Option Agreement (Selecta License Agreement) with Selecta that provides the Company with exclusive worldwide rights to Selecta's proprietary Synthetic Vaccine Particles (SVP™) platform technology for co-administration with gene therapy targets. Under the terms of the Selecta License Agreement, Selecta has granted the Company certain exclusive, worldwide, royalty-bearing licenses to Selecta's intellectual property and know-how relating to its SVP technology to research, develop and commercialize gene therapies for factor VIII, an essential blood clotting protein relevant to the treatment of hemophilia A, which is the initial target under the license. In addition, for a specified period of time, the Company may exercise options to research, develop and commercialize gene therapies utilizing the SVP technology for up to four additional targets, subject to the Company's payment of the applicable option exercise fee, in a range of $1.4 million to $2.0 million depending on the incidence of the applicable indication, to Selecta in each case.

Pursuant to a letter agreement (Letter Agreement), entered into between the Company and Selecta on June 6, 2017, Selecta agreed to reimburse the Company for all costs and expenses related to research and development for any licensed products for a specified amount of time, up to an agreed upon cap. Additionally, the Company has agreed to reimburse Selecta in respect of full-time equivalents and out-of-pocket costs incurred in performing certain tasks or assistance specifically requested by the Company. Selecta retains the responsibility to manufacture the Company's preclinical, clinical and commercial requirements for the SVP technology, subject to the terms of the Selecta License Agreement.

In connection with the execution of the Selecta License Agreement, the Company paid Selecta an upfront payment of $10.0 million in December 2016. Additional payments in the aggregate of $5.0 million were paid in June 2017 and October 2017 pursuant to the terms of the Selecta License Agreement and the Letter Agreement. On a target-by-target basis, the Company will be responsible to pay up to an aggregate of $430.0 million in milestone payments for each target, with up to $65.0 million being based on the Company's achievement of specified development and regulatory milestones and up to $365.0 million for commercial milestones, as well as tiered royalties on global net sales at percentages ranging from mid-single to low-double digits. For a period of three years, the Company has the right to fund up to 50% of any development or regulatory milestone payable to Selecta by issuing to Selecta shares of the Company's common stock having a fair market value equal to the percentage of such development or regulatory milestone, as applicable. The Selecta License Agreement will continue on a country-by-country and product-by-product basis until the expiration of the Company's royalty payment obligations with respect to such product in such country unless earlier terminated by the parties. The Selecta License Agreement may be terminated by the Company for convenience upon 90 days' notice and the Company will not be required to make any payments. Either party may terminate the Selecta License Agreement on a target-by-target basis for material breach with respect to such target.

In connection with the Selecta License Agreement, the Company entered into a Stock Purchase Agreement (SPA) with Selecta pursuant to which the Company purchased 197,238 unregistered shares of Selecta's common stock for $5.0 million in December 2016. An additional 324,362 unregistered shares of Selecta's common stock were purchased for $5.0 million in June 2017, and 205,254 unregistered shares of Selecta's common stock were purchased for $5.0 million in October 2017. These shares are classified as available-for-sale securities as of December 31, 2018.

In December 2016, the Company accounted for the payments under the Selecta License Agreement and SPA as a basket transaction and allocated the $15.0 million in cash payments to the shares of Selecta's common stock and the Selecta License Agreement in the amounts of $3.5 million and $11.5 million, respectively. The Company calculated the $3.5 million allocated for the Selecta shares acquired based on the closing market price on the date of purchase. The Company allocated the remaining $11.5 million to the Selecta License Agreement, which was expensed as acquired in-process research and development as the Company determined there was no alternative future use.

In June 2017, the Company accounted for the payments under the Selecta License Agreement, Letter Agreement and SPA as a basket transaction and allocated the $7.5 million in cash payments to the shares of Selecta's common stock and the Selecta License Agreement in the amounts of $4.4 million and $3.1 million, respectively. The Company calculated the $4.4 million allocated to the Selecta shares acquired based on the closing market price on the date of purchase. The Company allocated the remaining $3.1 million to the Selecta License Agreement, which was expensed

as acquired in-process research and development as the Company determined there was no alternative future use.
In October 2017, the Company accounted for the payments under the Selecta License Agreement, Letter Agreement and SPA as a basket transaction and allocated the $7.5 million in cash payments to the shares of Selecta's common stock and the Selecta License Agreement in the amounts of $4.1 million and $3.4 million, respectively. The Company calculated the $4.1 million allocated to the Selecta shares acquired based on the closing market price on the date of purchase. The Company allocated the remaining $3.4 million to the Selecta License Agreement, which was expensed as acquired in-process research and development as the Company determined there was no alternative future use.

Spark Therapeutics, Inc.
Notes to consolidated financial statements

(17) Income taxes

On December 22, 2017, the U.S. government enacted comprehensive tax legislation commonly referred to as the Tax Cuts and Jobs Act (the Tax Act). The Tax Act makes broad and complex changes to the U.S. tax code, including, but not limited to, reducing the U.S. federal corporate tax rate from 35 percent to 21 percent; eliminating the corporate alternative minimum tax (AMT) and changing how existing AMT credits can be realized; creating a new limitation on deductible interest expense; changing rules related to uses and limitations of net operating loss carryforwards created in tax years beginning after December 31, 2017; limitations on the deductibility of certain executive compensation; and changes to the calculation of the orphan drug credit.

In December 2017, the SEC issued Staff Accounting Bulletin No. 118 (SAB 118), which addresses situations where the accounting is incomplete for the income tax effects of the Tax Act. SAB 118 directs taxpayers to consider the impact of the Tax Act as "provisional" when the Company does not have the necessary information available, prepared or analyzed (including computations) to finalize the accounting for the change in tax law. Companies were provided a measurement period of up to one year to obtain, prepare, and analyze information necessary to finalize the accounting for provisional amounts or amounts that could not be estimated as of December 31, 2017.

With regards to the Tax Act impact on the tax provision as it relates to the Company for the year ended December 31, 2018, the Company has recognized the final impact of tax reform related to the revaluation of deferred tax assets and liabilities from 34% to 21% of $0.5 million of tax expense, which is offset by a reduction in the valuation allowance.

As a result of changes made by the Tax Act, starting with executive compensation paid in 2018, Section 162(m) of the Internal Revenue Code will limit the Company from deducting compensation, including performance-based compensation, in excess of $1.0 million paid to certain executives. The only exception to this rule is for compensation that is paid pursuant to a binding contract in effect on November 2, 2017 that would have otherwise been deductible under the prior Section 162(m) rules. The Company reviewed the binding contract requirement on the various compensation plans and determined that there was no impact of the law change to its deferred tax asset for stock compensation.

With regards to the one-time transition tax, the Company did not record any tax liability as the accumulated earnings and profits of foreign subsidiaries were in a deficit position. The Company reviewed the new international tax provisions included in the Tax Act and determined that no adjustments were necessary under ASC Topic 740, *Income Taxes*.

Income (loss) before income taxes attributable to domestic and international operations, consists of the following (in thousands):

	Year Ended December 31,		
	2016	2017	2018
Domestic	$(122,810)	$(239,301)	$(78,956)
Foreign	(843)	(15,144)	233
Loss before income taxes	$(123,653)	$(254,445)	$(78,723)

Income tax expense (benefit) consists of the following (in thousands):

	Year Ended December 31,		
	2016	2017	2018
Current tax:			
Domestic	$—	$—	$ —
Foreign	—	110	99
Deferred tax:			
Domestic	—	—	—
Foreign	—	(1,073)	—
Total income tax benefit (expense)	$—	$(963)	$ 99

A reconciliation of income tax benefit computed at the statutory federal income tax rate to income taxes as reflected in the consolidated financial statements is as follows:

Spark Therapeutics, Inc.
Notes to consolidated financial statements

	Year Ended December 31,		
	2016	2017	2018
Federal income tax benefit at statutory rate	34.0 %	34.0 %	21.0 %
State and local tax, net of federal benefit	10.4	10.3	7.5
Permanent differences	3.1	(0.3)	3.6
Tax credits	9.1	9.2	17.7
Tax Cuts and Jobs Act impact	—	(17.6)	(0.6)
Foreign rate differential	(0.1)	(1.3)	—
Change in valuation allowance	(56.5)	(33.9)	(42.9)
Change in tax reserve	—	—	(5.5)
Other	—	—	(0.9)
Effective income tax rate	— %	0.4 %	(0.1)%

Deferred taxes are recognized for temporary differences between the basis of assets and liabilities for financial statement and income tax purposes and for net operating loss and tax credit carryforwards. The significant components of the Company's deferred tax assets are comprised of the following (in thousands):

	December 31,	
	2017	2018
Deferred tax assets (liabilities):		
Net operating loss carryforwards	$114,152	$127,012
Tax credit carryforwards	51,586	60,174
Stock-based compensation	14,644	20,475
Deferred rent	4,697	1,149
Deferred revenue	956	—
Accruals and other	8,998	17,151
Fixed assets	—	1,875
Total deferred tax assets	195,033	227,836
Less valuation allowance	(193,796)	(227,836)
Net deferred tax assets	$1,237	$—
Fixed assets	(1,237)	—
Total deferred tax liabilities	$(1,237)	$—
Net deferred tax asset	$—	$—

As of December 31, 2018, the Company had U.S. federal net operating loss carryforwards of $318.3 million, which may be available to offset future income tax liabilities and will expire beginning in 2034. In addition, the Company had federal net operating loss carryforwards of $58.3 million that arose after the 2017 tax year, which are available to reduce future federal taxable income, if any, over an indefinite period. The utilization of those net operating loss carryforwards is limited to 80% of taxable income in any given year. As of December 31, 2018, the Company also had U.S. state net operating loss carryforwards of $376.4 million, which may be available to offset future income tax liabilities and will expire beginning in 2034, and foreign net operating losses of $8.6 million which can be carried forward indefinitely.

The Company has recorded a full valuation allowance against its net deferred tax assets as of December 31, 2017 and 2018 because the Company has determined that is it more likely than not that these assets will not be fully realized due to historic net operating losses incurred. The Company experienced a net change in valuation allowance of $86.2

million and $34.0 million in the years ended December 31, 2017 and 2018, respectively.

As of December 31, 2018, the Company had federal research and development and orphan drug tax credit carryforwards of $7.5 million and $52.7 million, respectively, available to reduce future tax liabilities, which expire beginning in 2034.

Under the provisions of the Internal Revenue Code, the net operating loss and tax credit carryforwards are subject to review and possible adjustment by the Internal Revenue Service and state tax authorities. Net operating loss and tax credit carryforwards may become subject to an annual limitation in the event of certain cumulative changes in the ownership interest

Spark Therapeutics, Inc.
Notes to consolidated financial statements

of significant shareholders over a three-year period in excess of 50%, as defined under Sections 382 and 383 of the Internal Revenue Code, respectively, as well as similar state provisions. This could limit the amount of tax attributes that can be utilized annually to offset future taxable income or tax liabilities. The amount of the annual limitation is determined based on the value of the Company immediately prior to the ownership change. Subsequent ownership changes may further affect the limitation in future years. The Company has completed financings since its inception which may have resulted in a change in control as defined by Sections 382 and 383 of the Internal Revenue Code, or could result in a change in control in the future.

The Company files tax returns as prescribed by the tax laws of the jurisdictions in which it operates. In the normal course of business, the Company is subject to examination by federal, state, and foreign jurisdictions, where applicable. The Company's tax years are still open under status from 2014 to present. All open years may be examined to the extent that tax credit or net operating loss carryforwards are used in future periods.

The Company recognizes in its consolidated financial statements the impact of a tax position, if it is more likely than not that such a position will be sustained on audit, based solely on the technical merits of the position. A reconciliation of the beginning and ending amounts of gross unrecognized tax benefits is as follows (in thousands):

	December 31, 2018
Gross unrecognized tax benefits at January 1	$ —
Increases related to prior year tax positions	3,858
Increases related to current year tax positions	483
Gross unrecognized tax benefits at December 31	$ 4,341

The Company recognizes interest and penalties related to uncertain tax positions in income tax expense. As of December 31, 2018, the Company had no accrued interest or penalties related to uncertain tax positions and no amounts have been recognized in the Company's consolidated statements of operations and comprehensive income (loss).

Spark Therapeutics, Inc.
Notes to consolidated financial statements

(18) Selected quarterly financial data (unaudited)

The following table contains quarterly financial information for 2017 and 2018 (in thousands). The Company believes that the following information reflects all normal recurring adjustments necessary for a fair presentation of the information for the periods presented. The operating results for any quarter are not necessarily indicative of results for any future period.

	2017 First quarter	Second quarter	Third quarter	Fourth quarter
Revenues	$1,274	$1,483	$1,900	$7,409
Research and development	32,348	32,989	39,342	30,481
Acquired in-process research and development	387	3,070	1,750	3,397
Impairment of acquired in-process research and development	—	15,696	—	—
Selling, general and administrative	21,414	26,729	26,640	36,341
Total operating expenses	54,149	78,484	67,732	70,219
Loss from operations	(52,875)	(77,001)	(65,832)	(62,810)
Net loss	$(52,289)	$(74,360)	$(65,012)	$(61,821)
Basic and diluted net loss per common share	$(1.70)	$(2.40)	$(1.90)	$(1.68)

	2018 First quarter	Second quarter	Third quarter	Fourth quarter
Revenues	$15,676	$25,185	$10,707	$13,157
Cost of goods sold	990	4,511	318	2,096
Research and development	30,109	25,524	32,829	36,792
Acquired in-process research and development	—	—	—	300
Selling, general and administrative	33,489	29,749	29,305	32,352
Total operating expenses	64,588	59,784	62,452	71,540
Loss from operations	(48,912)	(34,599)	(51,745)	(58,383)
Net (loss) income	$(46,373)	$80,165	$(47,357)	$(65,257)
Basic net (loss) income per common share	$(1.25)	$2.15	$(1.26)	$(1.73)
Diluted net (loss) income per common share	$(1.25)	$2.07	$(1.26)	$(1.73)

.

(19) Subsequent events

On February 22, 2019, the Company entered into an Agreement and Plan of Merger (Merger Agreement) with Roche Holdings, Inc., a Delaware corporation (Roche) and 022019 Merger Subsidiary, Inc., a Delaware corporation and wholly owned subsidiary of Roche (Merger Sub). Under the terms of the Merger Agreement, Merger Sub will commence a cash tender offer (Tender Offer) to acquire all of the issued and outstanding shares of common stock of the Company at a price per share equal to $114.50, net to the seller of such shares in cash, without interest, subject to any withholding of taxes required by applicable law. Following the completion of the Tender Offer, Merger Sub will merge with and into the Company, with the Company surviving as a wholly owned subsidiary of Roche (Merger). The Merger will be governed by Section 251(h) of the General Corporation Law of the State of Delaware, with no stockholder vote required to consummate the Merger. In the Merger, each outstanding share of the Company's

common stock (other than shares of common stock held by the Company as treasury stock, or owned

Spark Therapeutics, Inc.
Notes to consolidated financial statements

by Roche or Merger Sub or held by stockholders who are entitled to demand, and who properly demand, appraisal rights under Delaware law) will be converted into the right to receive $114.50 per share in cash, without interest, subject to any withholding of taxes required by applicable law. The transaction is expected to close in the second quarter of 2019.

The consummation of the Tender Offer and the Merger will be conditioned on (1) at least a majority of the shares of the Company's outstanding common stock having been validly tendered into and not withdrawn from the Tender Offer, (2) receipt of certain regulatory approvals, including expiration of the waiting period under the Hart-Scott-Rodino Antitrust Improvements Act of 1976, (3) the accuracy of certain representations and warranties that the Company made and compliance by the Company with certain covenants contained in the Merger Agreement, subject to qualifications, (4) there not having been a “Company Material Adverse Effect” (as defined in the Merger Agreement) with respect to the Company since the date of the Merger Agreement, and (5) other customary conditions. The Tender Offer and the Merger are not subject to a financing contingency.

The Merger Agreement may be terminated by the Company under certain circumstances, including in connection with an Acquisition Proposal (as defined in the Merger Agreement) that the Company’s Board of Directors determines constitutes a Superior Proposal (as defined in the Merger Agreement). Upon the termination of the Merger Agreement, under specified circumstances, the Company will be required to pay to Roche a termination fee of $144.0 million. The Company expects expenses will be incurred in connection with the closing of the transaction with Roche.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

Date: February 28, 2019

SPARK THERAPEUTICS, INC.

By: /s/ Jeffrey D. Marrazzo
Jeffrey D. Marrazzo
Chief Executive Officer
(Principal Executive Officer)

By: /s/ Stephen W. Webster
Stephen W. Webster
Chief Financial Officer
(Principal Financial Officer)

Pursuant to the requirements of the Securities and Exchange Act of 1934, this report has been signed by the following persons on behalf of the registrant in the capacities and on the dates indicated.

Signature	Title	Date
/s/ Jeffrey D. Marrazzo Jeffrey D. Marrazzo	Director and Chief Executive Officer (Principal Executive Officer)	February 28, 2019
/s/ Stephen W. Webster Stephen W. Webster	Chief Financial Officer (Principal Financial and Accounting Officer)	February 28, 2019
/s/ Katherine A. High, M.D. Katherine A. High, M.D.	Director	February 28, 2019
/s/ Steven M. Altschuler, M.D. Steven M. Altschuler, M.D.	Director	February 28, 2019
/s/ Lars Ekman, M.D., Ph.D. Lars Ekman, M.D., Ph.D.	Director	February 28, 2019
/s/ Anand Mehra, M.D. Anand Mehra, M.D.	Director	February 28, 2019
/s/ Vincent Milano Vincent Milano	Director	February 28, 2019
/s/ Robert Perez Robert Perez	Director	February 28, 2019
/s/ Elliott Sigal, M.D., Ph.D. Elliott Sigal, M.D., Ph.D.	Director	February 28, 2019
/s/ Lota Zoth, CPA Lota Zoth, CPA	Director	February 28, 2019