

METABASIS THERAPEUTICS INC

Form S-3

November 15, 2006

As filed with the Securities and Exchange Commission on November 15, 2006

Registration No. 333-

**UNITED STATES  
SECURITIES AND EXCHANGE COMMISSION**  
Washington, D.C. 20549

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**FORM S-3**

**REGISTRATION STATEMENT  
UNDER  
THE SECURITIES ACT OF 1933**

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**METABASIS THERAPEUTICS, INC.**

(Exact name of registrant as specified in its charter)

**Delaware**

(State or other jurisdiction of  
incorporation or organization)

**33-0753322**

(I.R.S. Employer  
Identification Number)

**11119 North Torrey Pines Road  
La Jolla, California 92037  
(858) 587-2770**

(Address, including zip code, and telephone number, including area code, of registrant's principal executive offices)

**Paul K. Laikind, Ph.D.  
President and Chief Executive Officer  
Metabasis Therapeutics, Inc.  
11119 North Torrey Pines Road  
La Jolla, California 92037  
(858) 587-2770**

(Name, address, including zip code, and telephone number, including  
area code, of agent for service)

Copies to:  
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**Approximate date of commencement of proposed sale to the public:**  
From time to time after the effective date of this Registration Statement.

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## Edgar Filing: METABASIS THERAPEUTICS INC - Form S-3

If the only securities being registered on this form are being offered pursuant to dividend or interest reinvestment plans, please check the following box. "

If any of the securities being registered on this form are to be offered on a delayed or continuous basis pursuant to Rule 415 under the Securities Act of 1933, other than securities offered only in connection with dividend or interest reinvestment plans, check the following box. X

If this form is filed to register additional securities for an offering pursuant to Rule 462(b) under the Securities Act, please check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering. "

If this form is a post-effective amendment filed pursuant to Rule 462(c) under the Securities Act, check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering. "

If this form is a registration statement pursuant to General Instruction I.D. or a post-effective amendment thereto that shall become effective upon filing with the Commission pursuant to Rule 462(e) under the Securities Act, check the following box. "

If this form is a post-effective amendment to a registration statement filed pursuant to General Instruction I.D. filed to register additional securities or additional classes of securities pursuant to Rule 413(b) under the Securities Act, check the following box. "

### CALCULATION OF REGISTRATION FEE

Title of Each Class of Securities to be Registered	Amount to be Registered (1)	Proposed Maximum Offering Price Per Unit (2)	Proposed Maximum Aggregate Offering Price (2)	Amount of Registration Fee
Common Stock, \$0.001 par value per share	6,046,471	(3) \$ 7.78	\$ 47,041,545	\$ 5,034

(1) Based upon the estimated maximum number of shares of common stock that may be sold by the selling stockholder. Pursuant to Rule 416(a) of the Securities Act, this Registration Statement shall also cover any additional shares of Registrant's Common Stock that become issuable by reason of any stock dividend, stock split, recapitalization or other similar transaction effected without receipt of consideration.

(2) Estimated solely for purposes of calculation of the registration fee in accordance with Rule 457(c) of the Securities Act. The price per share of common stock and the maximum aggregate offering price are based on the average of the high and low sale prices of Metabasis Therapeutics, Inc. common stock on November 10, 2006 as reported on the Nasdaq Global Market.

(3) Includes 260,000 shares of common stock that may be issued upon the exercise of a warrant.

The Registrant hereby amends this Registration Statement on such date or dates as may be necessary to delay its effective date until the Registrant shall file a further amendment which specifically states that this Registration Statement shall thereafter become effective in accordance with Section 8(a) of the Securities Act of 1933 or until the Registration Statement shall become effective on such date as the Securities and Exchange Commission acting pursuant to said Section 8(a) may determine.

The information in this prospectus is not complete and may be changed. The selling stockholder may not sell these securities or accept an offer to buy these securities until the registration statement filed with the Securities and Exchange Commission is effective. This prospectus is not an offer to sell these securities, and it is not soliciting offers to buy these securities in any state where such offer or sale is not permitted.

**SUBJECT TO COMPLETION, DATED NOVEMBER 15, 2006**

**PROSPECTUS**

**6,046,471 Shares of Common Stock**

This prospectus relates to the resale from time to time of up to 6,046,471 shares of our common stock that we may issue to the selling stockholder listed in the section entitled "Selling Stockholder" on page 31 of this prospectus. The shares of common stock offered under this prospectus by the selling stockholder are issuable to Kingsbridge Capital Limited, or Kingsbridge, pursuant to a common stock purchase agreement between us and Kingsbridge dated November 2, 2006, and a warrant we issued to Kingsbridge on that date. We are not selling any shares under this prospectus and will not receive any of the proceeds from the sale of shares by the selling stockholder.

The selling stockholder may sell the shares of common stock described in this prospectus in a number of different ways and at varying prices. We provide more information about how the selling stockholder may sell its shares of common stock in the section entitled "Plan of Distribution" on page 32 of this prospectus. We will not be paying any underwriting discounts or commissions in this offering.

Our common stock is currently traded on the Nasdaq Global Market under the symbol "MBRX". On November 14, 2006, the last reported sales price for our common stock was \$8.00 per share.

**Investment in our common stock involves a high degree of risk.**

**See the section entitled "Risk Factors" on page 5 of this prospectus.**

**Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or passed upon the adequacy or accuracy of this prospectus. Any representation to the contrary is a criminal offense.**

The date of this prospectus is

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You should rely only on the information contained in or incorporated by reference into this prospectus or any applicable prospectus supplement. We have not, and the selling stockholder has not, authorized anyone to provide you with different information. The selling stockholder is not making an offer of the common stock to be sold under this prospectus in any jurisdiction where the offer or sale is not permitted. You should not assume that the information contained in this prospectus or any applicable prospectus supplement is accurate as of any date other than the date on the front cover of this prospectus or the prospectus supplement, or that the information contained in any document incorporated by reference is accurate as of any date other than the date of the document incorporated by reference, regardless of the time of delivery of this prospectus or any sale of our common stock.

**PROSPECTUS SUMMARY**

*This prospectus contains forward-looking statements which involve risks and uncertainties. Our actual results could differ materially from those anticipated in these forward-looking statements as a result of certain factors referred to in Risk Factors and elsewhere in this prospectus.*

*The following summary does not contain all the information that may be important to you. You should read the entire prospectus, including the financial statements and other information incorporated by reference in this prospectus, before making an investment decision.*

**Metabasis Therapeutics, Inc.**

We are a biopharmaceutical company focused on the discovery, development and commercialization of novel drugs to address some of the world’s most widespread and costly chronic diseases involving pathways in the liver. These diseases include metabolic diseases such as diabetes, hyperlipidemia, a disease involving elevated levels of lipids such as cholesterol, and obesity, among others, and liver diseases such as hepatitis and primary liver cancer. We have established a broad and growing product pipeline targeting large markets with significant unmet medical needs. We have discovered all of our product candidates internally using our proprietary technologies.

We currently have five product candidates in clinical trials. These five product candidates, in order from the most advanced, are as follows:

Product Candidate	Disease Indication
pradefovir	hepatitis B
CS-917	type 2 diabetes
MB07133	primary liver cancer
MB07803	type 2 diabetes
MB07811	hyperlipidemia

Our agreements with collaborators may include joint marketing or promotion arrangements of our products. For example, we have retained co-promotion rights for CS-917 in North America with Daiichi Sankyo, Co. Ltd. Alternatively, we may grant exclusive marketing rights to our collaborators in exchange for up-front fees, milestones and royalties on future sales, if any. We have licensed worldwide commercialization rights for pradefovir to Valeant Pharmaceuticals International, which recently announced that it planned to sublicense pradefovir as part of an overall restructuring of Valeant’s operations. We have retained rights to MB07133, MB07803, MB07811 and all of the compounds generated from our current research programs, with the exception of product candidates covered by our collaborations with Merck & Co., Inc. and Idenix Pharmaceuticals, Inc. We intend to eventually market one or more of the product candidates for which we retain commercialization rights through our own sales force or with a co-promotion partner in the U.S. and through strategic collaborations abroad.

We were incorporated in Delaware in April 1997 as a wholly owned subsidiary of Gensia Sicor Inc., now Sicor Inc., which became an indirect wholly owned subsidiary of Teva Pharmaceutical Industries Limited in January 2004. In December 1997, Sicor assigned to us specified assets and liabilities relating to its then existing business of discovering and developing proprietary pharmaceutical products. Although we established a new business plan, pursued new opportunities and discovered new products and technologies following our inception, many of the assets we obtained in the transfer served as a foundation upon which we built our technologies and know-how. In June 1999, we completed a corporate restructuring and management stock purchase in which we became an independent company. We have a wholly owned subsidiary, Aramed, Inc., which was transferred to us by Sicor and does not conduct an active business.

Our principal offices are located at 11119 North Torrey Pines Road, La Jolla, California 92037, and our telephone number is (858) 587-2770. Our website address is <http://www.mbasis.com>. The information contained in, or that can be accessed through, our website is not part of this prospectus. Unless the context indicates otherwise, as used in this prospectus, the terms Metabasis, we, us and our refer to Metabasis Therapeutics, Inc., a Delaware corporation, and the terms selling stockholder and Kingsbridge refer to Kingsbridge Capital Limited. We use Metabasis, NuMimetic and HepDirect as trademarks in the U.S. and other countries. This prospectus also contains trademarks and tradenames of other companies.



### Equity Financing Facility With Kingsbridge

On November 2, 2006, we entered into a committed equity financing facility, or CEFF, with Kingsbridge, pursuant to which Kingsbridge committed to purchase, subject to certain conditions, up to \$50.0 million of our common stock. In connection with the CEFF, we entered into a common stock purchase agreement and registration rights agreement with Kingsbridge, both dated November 2, 2006, and on that date we also issued a warrant to Kingsbridge to purchase 260,000 shares of our common stock at an exercise price of \$9.26 per share. This warrant is exercisable beginning on May 2, 2007 and for a period of five years thereafter, subject to earlier termination in specified circumstances.

The common stock purchase agreement entitles us to sell and obligates Kingsbridge to purchase, from time to time over the 36-month period described below, shares of our common stock for cash consideration up to an aggregate of \$50.0 million, subject to specified conditions and restrictions. The shares of common stock that may be issued to Kingsbridge under the common stock purchase agreement and the warrant will be issued pursuant to an exemption from registration under the Securities Act of 1933, as amended, or the Securities Act. Pursuant to the registration rights agreement, we have filed a registration statement of which this prospectus is a part, covering the possible resale by Kingsbridge of any shares that we may issue to Kingsbridge under the common stock purchase agreement or upon exercise of the warrant. Through this prospectus, the selling stockholder may from time to time offer to the public for resale shares of our common stock that we may issue to Kingsbridge pursuant to the common stock purchase agreement, or that Kingsbridge may acquire upon exercise of the warrant.

For a period of 36 months from the first trading day following the effectiveness of the registration statement of which this prospectus is a part, we may, from time to time, at our discretion, and subject to specified conditions that we must satisfy, draw down funds under the CEFF by selling shares of our common stock to Kingsbridge. The purchase price of these shares will be at a discount of up to ten percent from the volume weighted average price of our common stock for each of the eight trading days following our election to sell shares, or draw down under the CEFF. The discount on each of these eight trading days will be determined as follows:

VWAP*	PERCENT OF VWAP	(APPLICABLE DISCOUNT)
Greater than \$9.50 per share	94	% (6 )%
Greater than \$5.75 per share but less than or equal to \$9.50 per share	92	% (8 )%
Equal to or greater than \$2.25 per share but less than or equal to \$5.75 per share	90	% (10 )%

\* As set forth in the common stock purchase agreement, VWAP means the volume weighted average price (the aggregate sales price of all trades of our common stock during each trading day divided by the total number of shares of common stock traded during that trading day) of our common stock during any trading day as reported by Bloomberg, L.P. using the AQR function. Except as described below, the VWAP and corresponding discount will be determined for each of the eight trading days during a draw down pricing period.

During the eight trading day pricing period for a draw down, if the VWAP for any one trading day is less than the greater of (i) \$2.25 or (ii) 90% of the closing price of our common stock on the trading day immediately preceding the beginning of the draw down period, the VWAP for that trading day will not be used in calculating the number of shares to be issued in connection with that draw down, and the draw down amount for that pricing period will be reduced by one-eighth of the draw down amount initially specified. In addition, if trading in our common stock is suspended for any reason for more than three consecutive or non-consecutive hours during any trading day during a draw down pricing period, that trading day will not be used in calculating the number of shares to be issued in connection with that draw down, and the draw down amount for that pricing period will be reduced by one-eighth of the draw down amount initially specified.

The maximum number of shares of common stock that we can issue pursuant to the CEFF is 6,046,471 shares, including 260,000 shares of common stock issuable upon exercise of the warrant that we issued to Kingsbridge in

connection with Kingsbridge's entry into the CEFF. We may exercise our right to draw down amounts under the CEFF, if and to the extent available, at such times as we have a need for additional capital and when we believe that sales of stock under the CEFF provide an appropriate means of raising capital.

Our ability to require Kingsbridge to purchase our common stock is subject to various limitations. The maximum dollar amount of shares that we may require Kingsbridge to purchase in any draw down pricing period under the CEFF is equal to the lesser of \$10 million or a specified percentage of our market capitalization at the time of a draw down under the CEFF. The specified percentage will be 1.5% if our market capitalization is equal to or exceeds \$175 million, 1% if our market capitalization is equal to or exceeds \$100 million but is less than \$175 million, or 0.75% if our market capitalization is equal to or exceeds \$65 million but is less than \$100 million.

Unless we and Kingsbridge agree otherwise, a minimum of three trading days must elapse between the expiration of any draw down pricing period and the beginning of the next succeeding draw down pricing period.

During the term of the CEFF, without the prior written consent of Kingsbridge, we may not (i) issue any rights, warrants or options to subscribe for or purchase our common stock, or any other securities directly or indirectly convertible into or exchangeable or exercisable into shares of our common stock, at an effective conversion, exchange or exercise price that varies or may vary with or is otherwise issuable in relation to the market price of our common stock, including by way of one or more resets to any fixed price; (ii) make any at-the-market offering (as defined in Rule 415(a)(4) under the Securities Act or any successor rule thereto) of our securities; and (iii) enter into any equity line or other form of financing that is substantially similar to the arrangement provided for in the CEFF. Except for the foregoing restrictions, the CEFF does not prohibit us from conducting additional debt or equity financings, other than during the eight trading day pricing period for a draw down. For the avoidance of confusion, except during the eight trading day pricing period for a draw down, the CEFF does not prohibit us from undertaking (i) a customary, firm-commitment underwritten public offering of our securities or (ii) a registered direct public offering or an unregistered private placement of our securities where the price per share of such securities is fixed concurrently with the execution of definitive documentation relating to the offering or placement, as applicable.

The issuance of our common stock under the CEFF or upon exercise of the Kingsbridge warrant will have no effect on the rights or privileges of existing holders of common stock except that the voting interests and potentially the economic interests of existing stockholders will be diluted as a result of the issuance. Although the number of shares of common stock that stockholders presently own will not decrease, these shares will represent a smaller percentage of our total shares that will be outstanding after any issuances of shares of common stock to Kingsbridge. If we draw down amounts under the CEFF when our stock price is decreasing, we will need to issue more shares to raise the same amount than if our stock price was higher. Such issuances will have a dilutive effect and may further decrease our stock price.

Kingsbridge agreed in the common stock purchase agreement that during the term of the CEFF, neither Kingsbridge nor any of its affiliates, nor any entity managed or controlled by it, will enter into or execute, or cause any person or entity to enter into or execute, any short sale of any shares of our common stock.

Before Kingsbridge is obligated to buy any shares of our common stock pursuant to a draw down, the following conditions, none of which is in the control of Kingsbridge, must be met as of the draw down exercise date and the date upon which each settlement of the purchase and sale of our common stock occurs:

- Each of our representations and warranties in the common stock purchase agreement must be true and correct in all material respects as of the date when made as though made at that time, except for representations and warranties that are expressly made as of a particular date.
- We must have performed, satisfied and complied in all material respects with all covenants, agreements and conditions required by the common stock purchase agreement, the registration rights agreement and the warrant to be performed, satisfied or complied with by us.
- We must have complied in all respects with all applicable federal, state and local governmental laws, rules, regulations and ordinances in connection with the execution, delivery and performance of the common stock purchase agreement and the consummation of the transactions contemplated by it, except for any noncompliance that generally would not have a material adverse effect on our business.





- The registration statement, which includes this prospectus, shall have previously become effective and shall remain effective, and neither we nor Kingsbridge shall have received notice that the Securities and Exchange Commission, or SEC, has issued or intends to issue a stop order with respect to the registration statement or otherwise has suspended or withdrawn its effectiveness or intends or has threatened to do so, and no other suspension of the use of or withdrawal of the effectiveness of the registration statement or this prospectus shall exist.
- We shall not have knowledge of any event that could reasonably be expected to have the effect of causing the registration statement applicable to the resale of shares of our common stock by Kingsbridge to be suspended or otherwise ineffective.
- Trading in our common stock shall not have been suspended by the SEC, the Nasdaq Global Market or the National Association of Securities Dealers and trading in securities generally on the Nasdaq Global Market shall not have been suspended or limited.
- No statute, rule, regulation, executive order, decree, ruling or injunction shall have been enacted, entered, promulgated or endorsed by any court or governmental authority which prohibits the consummation of any of the transactions contemplated by the common stock purchase agreement.
- No action, suit or proceeding before any arbitrator or any governmental authority shall have been commenced, and no investigation by any governmental authority shall have been threatened, against us or any of our officers, directors or affiliates seeking to enjoin, prevent or change the transactions contemplated by the common stock purchase agreement.
- We shall have sufficient shares of common stock, calculated using the closing price of our common stock as of the trading day immediately preceding a draw down, registered under the registration statement to issue and sell such shares in accordance with such draw down.
- We shall not be in default in any material respect under the warrant to purchase 260,000 shares of our common stock issued to Kingsbridge in connection with the CEFF.

There is no guarantee that we will be able to meet the foregoing conditions or any other conditions under the common stock purchase agreement or that we will be able to draw down any portion of the amounts available under the CEFF.

Pursuant to our registration rights agreement with Kingsbridge, we have filed a registration statement, which includes this prospectus, with the SEC relating to the resale by Kingsbridge of any shares of common stock purchased by Kingsbridge under the common stock purchase agreement or issued to Kingsbridge as a result of the exercise of the Kingsbridge warrant. As described more fully above, the effectiveness of this registration statement is a condition precedent to our ability to sell common stock to Kingsbridge under the common stock purchase agreement. We are entitled in certain circumstances, including the existence of certain kinds of nonpublic information, to deliver a blackout notice to Kingsbridge to suspend the use of this prospectus and prohibit Kingsbridge from selling shares under this prospectus. If we deliver a blackout notice in the 15 trading days following the settlement of a draw down, or if the registration statement of which this prospectus is a part is not effective in circumstances not permitted by the registration rights agreement, then we must pay specified amounts to Kingsbridge (or issue Kingsbridge additional shares in lieu of payment) as liquidated damages.

The foregoing summary of the CEFF does not purport to be complete and is qualified by reference to the common stock purchase agreement, the registration rights agreement and the warrant, copies of which have been filed as exhibits to the registration statement of which this prospectus is a part.

## RISK FACTORS

*Investing in our common stock involves a high degree of risk. Before deciding whether to invest in our common stock, you should consider carefully the risk factors described below, as well as in our subsequent filings with the SEC. If any of these risks actually occurs, our business, financial condition, results of operations or cash flow could be seriously harmed. This could cause the trading price of our common stock to decline, resulting in a loss of all or part of your investment.*

### **Risks Related to our Business**

***We are dependent on the success of one or more of our current product candidates and we cannot be certain that any of them will receive regulatory approval or be commercialized.***

We have expended significant time, money and effort in the development of our five current product candidates, pradefovir, CS-917, MB07133, MB07803, and MB07811. Clinical trials conducted to date in patients treated with pradefovir have provided evidence of efficacy as measured by various parameters that we believe to be clinically and statistically significant. However, no pivotal, adequate and well-controlled clinical trials designed to provide clinical and statistically significant proof of efficacy, or to provide sufficient evidence of safety to justify approval, have been completed with any of our products. All of our product candidates will require additional development, clinical trials and regulatory clearances before they can be commercialized. Positive results from preclinical studies and early clinical trials do not necessarily mean later clinical trials will succeed. Our product development efforts may not lead to commercial drugs, either because our product candidates fail to be safe and effective in clinical trials or because we have inadequate financial or other resources to pursue our product candidates through the clinical trial and approval processes. If any of our product candidates fail to demonstrate safety or efficacy at any time or during any phase of development, we would experience potentially significant delays in, or be required to abandon, development of the product candidate.

We do not anticipate that any of our current product candidates will be eligible to receive regulatory approval and begin commercialization for a number of years, if at all. Even if we were ultimately to receive regulatory approval for these product candidates, we and/or our partners, as applicable, may be unable to commercialize them successfully for a variety of reasons. These include, for example, the availability of alternative treatments, lack of cost effectiveness, the cost of manufacturing the product on a commercial scale and the effect of competition with other drugs. The success of our product candidates may also be limited by the prevalence and severity of any adverse side effects. If we fail to commercialize one or more of our current product candidates, we may be unable to generate sufficient revenues to attain or maintain profitability, and our reputation in our industry and the investment community may be damaged.

***If clinical trials of our product candidates do not produce successful results, we and our commercialization collaborators, as applicable, will be unable to commercialize these products.***

To receive regulatory approval for the commercialization of pradefovir, CS-917, MB07133, MB07803, MB07811 or any other product candidates that we may develop, adequate and well-controlled clinical trials must be conducted to demonstrate safety and efficacy in humans to the satisfaction of the U.S. Food and Drug Administration, or FDA, in the U.S. and other regulatory agencies elsewhere in the world. In order to support marketing approval, these agencies typically require successful results in one or more Phase 3 clinical trials, which our current product candidates have not yet reached and may never reach. Clinical testing is expensive, can take many years and has an uncertain outcome. Failure can occur at any stage of the testing. We may experience numerous unforeseen events during, or as a result of, the clinical trial process that could delay or prevent commercialization of our current or future product candidates, including the following:

- clinical trials may produce negative or inconclusive results,
- patient recruitment and enrollment in clinical trials may be slower than we anticipate,
- costs of clinical trials may be greater than we anticipate,

- our product candidates may cause undesirable side effects that delay or preclude regulatory approval or limit their commercial use or market acceptance if approved,
- collaborators who are responsible for clinical trials of our product candidates may not devote sufficient resources to these clinical trials or conduct them in a timely manner, or
- we may face delays in obtaining regulatory approvals to commence a clinical trial.

Success in preclinical testing and early clinical trials does not mean that later clinical trials will be successful because product candidates in later-stage clinical trials may fail to demonstrate sufficient safety and efficacy despite having progressed through initial clinical testing. Our clinical experience with our product candidates is limited, and to date our product candidates have been tested in less than the number of patients that will likely need to be studied to gain regulatory approval. The data collected from clinical trials with larger patient populations may not demonstrate sufficient safety and efficacy to support regulatory approval of these product candidates.

The targeted endpoints for clinical trials of pradefovir and CS-917 have been, and will continue to be, primarily established by Valeant (and/or possibly a future collaborator on the development of pradefovir) and Daiichi Sankyo, respectively. We are solely responsible for establishing the targeted endpoints for clinical trials of MB07133, MB07803 and MB07811. These targeted endpoints may be inadequate to demonstrate the safety and efficacy levels required for regulatory approvals. Even if we believe data collected from clinical trials of our product candidates are promising, such data may not be sufficient to support marketing approval by the FDA or other regulatory agencies abroad. Further, preclinical and clinical data can be interpreted in different ways, and the FDA or other foreign regulatory agencies may interpret such data in different ways than us or our collaborators. Our failure to adequately demonstrate the safety and efficacy of our product candidates would prevent our receipt of regulatory approval, and ultimately the commercialization of these product candidates.

***Our product candidates may cause undesirable side effects that could delay or prevent their regulatory approval or commercialization or have other significant adverse implications on our business.***

Prior to receiving regulatory approval, undesirable side effects caused by our product candidates could interrupt, delay or halt clinical trials and could result in the denial of regulatory approval by the FDA or other regulatory authorities for any or all targeted indications, and in turn prevent us from commercializing our product candidates and generating revenues from their sale.

For example, the inhibition of gluconeogenesis can cause elevated levels of lactic acid, or lactate, which, if high and sustained under certain conditions, could lead to lactic acidosis, a serious and potentially fatal condition. Certain preclinical animal studies have shown that CS-917 raises lactate levels two- to three-fold in some but not all animal models. Elevated lactate levels have also been observed in certain human clinical trials of CS-917. For example, in a 28-day Phase 2 clinical trial of CS-917, isolated instances of lactate elevation significantly above the normal range were seen in some patients in both CS-917 and placebo treated groups over the course of the 28 days. No patient exhibited sustained lactate levels significantly above the normal range over a period of consecutive days during the clinical trial. However, one patient who received 200 milligrams of CS-917 twice a day was withdrawn from the clinical trial by the investigator on day 15 due to concerns over consistently elevated lactate levels measured the previous day. Other incidences of elevated lactate levels have been observed and will likely occur in the future.

Our product candidates could also exhibit adverse interactions with other drugs. For instance, in March 2005, we were notified by Daiichi Sankyo that two serious adverse events involving lactic acidosis had occurred in two patients in a Phase 1 clinical trial evaluating the interaction of CS-917 with metformin. The serious adverse events were resolved after medical intervention. The two patients were administered CS-917 in combination with metformin. At high blood levels, metformin is believed to cause mitochondrial toxicity, a cellular toxicity, which can cause lactic acidosis. These dangerous levels are known to occur in patients with significant renal dysfunction who are inappropriately given metformin. Consequently, metformin is contraindicated for use in patients with significant renal dysfunction. After the adverse events occurred, three clinical trials that were ongoing

at the time were stopped while one Phase 1 clinical trial which did not combine CS-917 with metformin continued and was completed. It was subsequently determined that the two patients who experienced the lactic acidosis had blood levels of metformin that were elevated compared to other patients in the clinical trial who received metformin before administration of CS-917. After CS-917 administration, when the two patients were being administered metformin and CS-917, the metformin blood levels increased significantly into a range that is associated with mitochondrial toxicity and subsequent lactic acidosis. CS-917 blood levels also rose higher than expected.

The reason for the unexpectedly high blood levels of both drugs in these two patients is unknown at this time. In July 2005, after completing a comprehensive review of the program and the events and data surrounding the two serious adverse events, we and Daiichi Sankyo concluded that the lactic acidosis observed in the two patients was likely due to the significantly increased blood levels of metformin described above which in turn likely led to mitochondrial toxicity. Subsequently, Daiichi Sankyo decided that Phase 2b clinical trials of CS-917 could safely resume. In February 2006, after submission of the proposed clinical trial protocol to the FDA and approval by institutional review boards, or IRBs, a Phase 2b clinical trial of CS-917 was initiated. This Phase 2b clinical trial provides for measurement of HbA1c, the endpoint generally required for approval of diabetes product candidates by regulatory agencies. Daiichi Sankyo has conducted and will likely conduct additional studies combining CS-917 with other diabetes drugs to assess both the safety and eventually the potential for enhanced efficacy with the combination. However, further use of CS-917 in combination with metformin will be avoided unless additional data suggests that the elevation of metformin blood levels as seen in the two patients can be avoided through patient exclusion or through the administration of CS-917 at lower doses or through other means. Should CS-917 eventually be approved and the use of CS-917 in combination with metformin remains an issue, the FDA may require additional measures be taken during marketing, such as prominent warning labels known as black-box warnings, physician education programs and/or other steps regarding concomitant use of CS-917 and metformin.

In February 2006, we initiated Phase 1 clinical trials of our second-generation product candidate for diabetes, MB07803, which works by the same mechanism as CS-917.

It is also possible that CS-917 and MB07803 may cause other side effects. In certain preclinical studies, as expected based on the mechanism of these compounds, fasted animals treated with CS-917 showed pronounced hypoglycemia, a condition involving abnormally low blood glucose levels that can lead to coma or death. Hypoglycemia has been observed in one patient participating in a clinical trial that involved multi-day administration of the highest dose of CS-917 tested to date in patients (400 milligrams twice a day). This dose is above what is expected to be used in Phase 3 clinical trials if warranted. However, we cannot yet rule out the possibility that CS-917 may increase a patient's susceptibility to hypoglycemia, including the potential for severe hypoglycemia, by inhibiting gluconeogenesis, especially in elderly patients who are already prone to develop this condition. Some rodent models of diabetes studied in preclinical trials of CS-917 demonstrated, at glucose lowering doses, increased levels of fat molecules known as triglycerides, which are associated with an increased risk of cardiovascular disease. Elevated triglyceride levels have not been observed in human clinical trials to date. Other side effects observed during early clinical trials of CS-917 included nausea and vomiting.

We apply our HepDirect technology to make liver-specific prodrugs of certain compounds. A prodrug is a drug to which a chemical modification has been made that renders it inactive until enzymes in the body convert it to its active form. When converted by the body to their active forms, HepDirect prodrugs produce a byproduct that is within a class of compounds that have the potential of causing toxicity, genetic mutations and cancer. We are unaware of any byproduct-related toxicities demonstrated to date in clinical trials of either pradevovir or MB07133. However, we cannot be certain that this byproduct will not cause adverse effects in current or future clinical trials of these product candidates or other HepDirect prodrugs we may develop. In addition, because our current product candidates are in early stages of development and have been tested in relatively small populations, additional side effects may be observed as their development progresses.

MB07811 is a HepDirect prodrug of a potent liver-selective thyroid hormone receptor modulator (a mimetic) discovered by us. Thyroid hormone and thyroid hormone mimetics are known to exhibit a wide array of physiological actions involving a variety of organs that can be assessed in pre-clinical animal studies. Both beneficial and undesirable effects can be inferred from studies of humans with hyperthyroidism (elevated thyroid hormone). The development of liver-selective thyroid receptor modulators for the treatment of hyperlipidemia is a novel approach seeking to exploit the beneficial hepatic effects while avoiding toxicities related

to systemic exposure of thymimetic agents. Successful development of MB07811 will require finding a dose range in humans that provides adequate benefit and an acceptable safety profile, that is known as an acceptable Therapeutic Index.

In addition, undesirable side effects seen in the clinical trials of our product candidates may have other significant adverse implications on our business, for example:

- we may be unable to obtain additional financing on acceptable terms, if at all,
- our stock price could decline,
- our collaborators may ultimately terminate development of our partnered products, may further decide not to develop backup product candidates and may terminate our agreements,
- if these agreements were terminated we may determine not to further develop the affected product candidates due to resource constraints and may not be able to establish additional collaborations for their further development on acceptable terms, if at all,
- if we were to later continue the clinical trials of these product candidates and receive regulatory approval, earlier findings may significantly limit their marketability and thus significantly lower our potential future revenues from their sale,
- we may be subject to product liability or stockholder litigation, and
- we may be unable to attract and retain key employees.

In addition, if any of our product candidates receive marketing approval and we or others later identify undesirable side effects caused by the product:

- regulatory authorities may withdraw their approval of the product, or we may decide to cease marketing and sale of the product voluntarily,
- we may be required to change the way the product is administered, conduct additional clinical trials, change the labeling of the product, or change the product's manufacturing facilities, and
- our reputation may suffer.

Any of these events could prevent us from achieving or maintaining market acceptance of the affected product or could substantially increase the costs and expenses of commercializing the product, which in turn could delay or prevent us from generating significant revenues from the sale of the product.

***We are currently dependent on our collaborations with Valeant and Daiichi Sankyo for development of pradeфовir and CS-917, respectively, and events involving these collaborations, our collaborations with Merck and Idenix, or any future collaborations could prevent us from developing and commercializing our product candidates and achieving or sustaining profitability.***

We have entered into collaborations with Valeant and Daiichi Sankyo for the development and commercialization of pradeфовir and CS-917, respectively. Valeant and Daiichi Sankyo have agreed to finance the clinical trials for pradeфовir and CS-917, respectively, and, if they are approved, manufacture and market them. In April 2006, Valeant announced that it planned to sublicense pradeфовir as part of an overall restructuring of Valeant's operations. Accordingly, we are currently dependent on Valeant and Daiichi Sankyo to gain FDA and other foreign regulatory agency approval of, and to commercialize, pradeфовir and CS-917, and may be similarly dependent on any future sublicensee of pradeфовir. We have also entered into two collaborations with Merck and a collaboration with Idenix. The first collaboration with Merck seeks to develop and commercialize new products for the treatment of hepatitis C infection and the second seeks to develop and commercialize new products to treat



several metabolic diseases including type 2 diabetes, hyperlipidemia and obesity. Our collaboration with Idenix seeks to develop and commercialize new products for the treatment of hepatitis C infection. Although our collaboration with Merck has not yet yielded any product candidates and our collaboration with Idenix was only recently initiated, should a candidate ultimately be selected, we will be dependent on Merck and/or Idenix for further development and commercialization of any resulting product candidates. In addition, since we do not currently possess the resources necessary to independently develop and commercialize all of the potential products that may be based upon our technologies, including MB07133, MB07803 and MB07811 we may need to enter into additional collaborative agreements to assist in the development and commercialization of some of these potential products. However, our discussions with potential collaborators may not lead to the establishment of new collaborations on acceptable terms, if at all, or it may take longer than expected to establish new collaborations, leading to development and commercialization delays.

We have limited control over the amount and timing of resources that Valeant, Daiichi Sankyo, Merck, Idenix or any future collaborators devote to our programs or potential products. These collaborators may breach or terminate their agreements with us or otherwise fail to conduct their collaborative activities successfully and in a timely manner. Further, our collaborators may not develop products that arise out of our collaborative arrangements or devote sufficient resources to the development, manufacture, marketing or sale of these products. In the event that one of our collaborations is terminated, and we believe that the continued development or commercialization of a product candidate or drug compound covered by the collaboration is warranted, we may seek to obtain rights to develop and commercialize the product candidate or drug compound, if we did not already have those rights. We would then determine whether to continue the development or commercialization of the product candidate or drug compound independently or together with a new collaborator. However, in the event that we do not have sufficient resources to independently develop or commercialize the product candidate or drug compound, and we cannot establish a new collaboration on acceptable terms, we would be forced to discontinue its development or commercialization.

Our agreement with Daiichi Sankyo contains certain rights and restrictions regarding our access to and use of confidential data and information generated by Daiichi Sankyo. We have initiated Phase 1 clinical trials of MB07803, a second-generation gluconeogenesis inhibitor to which Daiichi Sankyo has no rights and that may be a direct competitor to CS-917. Because of this competitive situation and with our consent, the transfer to us of confidential information and data related to CS-917 from Daiichi Sankyo has already been reduced and we expect that further reductions in information flow will occur. This situation may limit our ability to (i) provide information regarding clinical results unless they are publicly released by Daiichi Sankyo, (ii) influence decisions made at Daiichi Sankyo regarding CS-917 and (iii) accurately track Daiichi Sankyo's diligence on the development program.

We and our present and future collaborators may fail to develop or effectively commercialize products or drug compounds covered by our present and future collaborations if:

- we do not achieve our objectives under our collaboration agreements,
- we are unable to obtain patent protection for the product candidates or proprietary technologies we discover in our collaborations,
- we are unable to manage multiple simultaneous product discovery and development collaborations,
- our potential collaborators are less willing to expend their resources on our programs due to their focus on other programs or as a result of general market conditions,
- our collaborators become competitors of ours or enter into agreements with our competitors,
- we or our collaborators encounter regulatory hurdles that prevent commercialization of our product candidates,
- we develop products and processes or enter into additional collaborations that conflict with the business objectives of our other collaborators,



- consolidation in our target markets limits the number of potential collaborators, or
- we are unable to negotiate additional collaboration agreements under terms satisfactory to us.

If we are unable to develop or commercialize our products as a result of the occurrence of any of these events, we may not be able to generate sufficient revenues to achieve or maintain profitability.

*Any future sublicense of pradefovir may not occur on favorable terms to us, if at all.*

In April 2006, Valeant announced that it planned to sublicense pradefovir as part of an overall restructuring of Valeant's operations. Valeant has advised us that it plans to continue the development of pradefovir through the initiation of Phase 3 clinical trials while Valeant seeks to identify a partner to complete the development and potential commercialization of pradefovir for the treatment of hepatitis B virus, or HBV. In addition, any sublicense of pradefovir is subject to our consent, which may not be unreasonably withheld. We may disagree with Valeant regarding the sublicense, which may result in delays in the development of pradefovir. Any sublicense of pradefovir by Valeant may not occur on favorable terms to us, if at all, which may adversely impact the future development of pradefovir and may harm our business results.

*Because our collaborations with Merck may involve Merck's proprietary compounds, if Merck terminates development of product candidates we may not have the right to pursue development of these product candidates on our own.*

The objective of our hepatitis C collaboration with Merck has been to discover product candidates for the treatment of this disease by applying our technology to certain compounds. The funded research phase of this collaboration has ended. Merck has evaluated and may continue to evaluate the drug compounds discovered under the research phase of the collaboration to determine if one or more will be recommended for clinical development. If Merck so designates a product candidate and then subsequently terminates this collaboration before a defined stage of development of that product candidate, which it may do without cause at any time upon 90 days' advance written notice to us, we will not have any right to develop or commercialize that product candidate. In addition, if this collaboration with Merck terminates and Merck successfully develops products based on these proprietary compounds without applying our technology, we will not be entitled to milestone payments or royalties with respect to those products.

Our agreement with Merck to develop and commercialize new products to treat several metabolic diseases including type 2 diabetes, hyperlipidemia and obesity may include the development of compounds owned or controlled by Merck. Accordingly, if Merck terminates this collaboration it may prove difficult for us to continue development of such compounds.

*Conflicts may arise between us and any of our collaborators that could delay or prevent the development or commercialization of our product candidates.*

Conflicts may arise between our collaborators and us, such as conflicts concerning the interpretation of clinical data, the achievement of milestones or the ownership of intellectual property developed during the collaboration. If any conflicts arise with Valeant, Daiichi Sankyo, Merck, Idenix or any future collaborators, they may act in their self-interest, which may be adverse to our best interests. Any such disagreement between us and a collaborator could result in one or more of the following, each of which could delay or prevent the development or commercialization of our product candidates, and in turn prevent us from generating sufficient revenues to achieve or maintain profitability:

- unwillingness on the part of a collaborator to pay us research funding, milestone payments or royalties we believe are due to us under our collaboration agreement,
- uncertainty regarding ownership of intellectual property rights arising from our collaborative activities, which could prevent us from entering into additional collaborations, or disagreements with our collaborators regarding the protection of intellectual property rights,

- unwillingness on the part of a collaborator to keep us informed regarding the progress of its development and commercialization activities or to permit public disclosure of the results of those activities, or
- slowing or cessation of a collaborator's development or commercialization efforts with respect to our product candidates.

***Our efforts to discover product candidates beyond our current product candidates may not succeed, and any product candidates we recommend for clinical development may not actually begin clinical trials.***

We intend to use our proprietary technologies and our knowledge and expertise to develop and commercialize novel drugs to address some of the world's most widespread and costly chronic diseases involving pathways in the liver. Our goal is to expand our clinical development pipeline by continuing to recommend new drug compounds for clinical development. However, the process of researching and discovering drug compounds is expensive, time-consuming and unpredictable. Data from our current research programs may not support the clinical development of our lead compounds or other compounds from these programs, and we may not identify any additional drug compound suitable for recommendation for clinical development. Moreover, any drug compounds we recommend for clinical development may not demonstrate, through preclinical testing, indications of safety and potential efficacy, that such drug compounds warrant advancement into clinical trials. Such findings would potentially impede our ability to maintain or expand our clinical development pipeline. Our ability to identify new drug compounds and advance them into clinical development also depends upon our ability to fund our research and development operations, and we cannot be certain that additional funding will be available on acceptable terms, or at all.

***Delays in the commencement or completion of clinical trials could result in increased costs to us and delay our ability to generate significant revenues.***

Delays in the commencement or completion of clinical trials could significantly impact our product development costs. We do not know whether planned clinical trials will begin on time or be completed on schedule, if at all. The commencement of clinical trials can be delayed for a variety of reasons, including:

- delays in obtaining regulatory approval to commence a clinical trial,
- delays in reaching agreement on acceptable terms with prospective contract research organizations and clinical trial sites,
- delays in manufacturing sufficient quantities of a product candidate or other materials necessary to conduct the clinical trial,
- delays in obtaining institutional review board approval to conduct a clinical trial at a prospective site,
- delays in recruiting and enrolling patients to participate in a clinical trial, and
- the failure of our collaborators to adequately resource our product candidates due to their focus on other programs or as a result of general market conditions.

In addition, once a clinical trial has begun, it may be suspended or terminated by us, our collaborators, the FDA or other regulatory authorities due to a number of factors, including:

- failure to conduct the clinical trial in accordance with regulatory requirements or clinical protocols,
- inspection of the clinical trial operations or clinical trial site by the FDA or other regulatory authorities resulting in the imposition of a clinical hold,



- unforeseen safety issues, or
- lack of adequate funding to continue the clinical trial.

If we experience significant delays in the commencement or completion of clinical testing, our product development costs may increase, we may lose any competitive advantage associated with early market entry and our ability to generate significant revenues may be delayed. In addition, many of the factors that cause, or lead to, a delay in the commencement or completion of clinical trials may also ultimately lead to the denial of regulatory approval of a product candidate.

***We rely on third parties to conduct our clinical trials. If these third parties do not successfully meet their obligations under our agreements, we may not be able to obtain regulatory approval for or commercialize our product candidates.***

Valeant and Daiichi Sankyo are currently responsible for conducting clinical trials of pradefovir and CS-917, respectively. Although our collaborations with Merck to discover product candidates for the treatment of hepatitis C and metabolic diseases including type 2 diabetes, hyperlipidemia and obesity have not yet yielded product candidates, should they be successful, we will be dependent on Merck to conduct clinical trials of any resulting product candidates. Similarly, our collaboration with Idenix to discover product candidates for the treatment of hepatitis C was recently initiated and therefore has not yet yielded product candidates. Should our collaboration with Idenix be successful, we will be dependent on Idenix to conduct clinical trials of any resulting product candidates. We intend to rely on other third parties, such as contract research organizations, medical institutions, clinical investigators and contract laboratories, to conduct our clinical trials of MB07133, MB07803, MB07811 and any other product candidates that we may develop for which a collaborator is not responsible for clinical development. If Valeant, Daiichi Sankyo, Merck, Idenix or these other third parties do not successfully meet their obligations under our agreements, or if the quality or accuracy of the clinical data they obtain is compromised due to the failure to adhere to clinical protocols or for other reasons, clinical trials may be extended, delayed or terminated, and these product candidates may not receive regulatory approval or be successfully commercialized.

***Because our product candidates, research programs and collaborative efforts depend on our proprietary technologies, adverse events affecting our proprietary technologies may delay or prevent the commercialization of our product candidates.***

We used our HepDirect technology to discover pradefovir, MB07133, MB07811 and applied this technology in certain other programs as well. We used our NuMimetic technology to identify CS-917 and MB07803. We intend to use these and future proprietary technologies to expand our product pipeline in the future. We also may leverage our HepDirect and other liver-targeting technology through strategic alliances and collaborations with other companies, such as our hepatitis C collaborations with Merck and Idenix in which we are applying our technology to certain Merck and Idenix compounds. Our proprietary technologies are subject to many of the same risks as our product candidates, including risks related to:

- obtaining and maintaining patent and trade secret protection for these technologies,
- avoiding infringement of the proprietary rights of third parties,
- the development of competing technologies by others, and
- in HepDirect's case, the safety and effectiveness of this technology in humans.

Because certain of our product candidates and research programs are dependent on our proprietary technologies, adverse events affecting our proprietary technologies may in turn delay or prevent the development or commercialization of our product candidates, which could impede our ability to generate revenues and achieve or maintain profitability.

***Our product candidates are subject to extensive regulation, which can be costly and time consuming, cause unanticipated delays or prevent the receipt of the required approvals to commercialize our product candidates.***

The clinical development, manufacturing, labeling, storage, record-keeping, advertising, promotion, export, marketing and distribution of our product candidates are subject to extensive regulation by the FDA and other regulatory agencies in the U.S. and by comparable governmental authorities in foreign markets. In the U.S., neither we, nor our collaborators, are permitted to market our product candidates until we or our collaborators receive approval of a New Drug Application, or NDA, from the FDA or receive similar approvals abroad. The process of obtaining these approvals is expensive, often takes many years, and can vary substantially based upon the type, complexity and novelty of the product candidates involved. Approval policies or regulations may change. In addition, as a company, we have not previously filed NDAs with the FDA or filed similar applications with other foreign regulatory agencies. This lack of experience may impede our ability to obtain FDA or other foreign regulatory agency approval in a timely manner, if at all, for our product candidates for which development and commercialization is our responsibility.

Despite the time and expense invested, regulatory approval is never guaranteed. The FDA or other foreign regulatory agencies can delay, limit or deny approval of a product candidate for many reasons, including:

- a product candidate may not be safe and effective,
- FDA or other foreign regulatory agency officials may not find the data from preclinical testing and clinical trials sufficient,
- the FDA or other foreign regulatory agency may not approve of our third-party manufacturers' processes or facilities, or
- the FDA or other foreign regulatory agency may change its approval policies or adopt new regulations.

Any delay in obtaining, or inability to obtain, these approvals would prevent us from commercializing our product candidates.

***Even if any of our product candidates receive regulatory approval, our product candidates may still face future development and regulatory difficulties.***

If any of our product candidates receive regulatory approval, the FDA or other foreign regulatory agencies may still impose significant restrictions on the indicated uses or marketing of the product candidates or impose ongoing requirements for potentially costly post-approval studies. In addition, regulatory agencies subject a product, its manufacturer and the manufacturer's facilities to continual review and periodic inspections. If a regulatory agency discovers previously unknown problems with a product, including adverse events of unanticipated severity or frequency, or problems with the facility where the product is manufactured, a regulatory agency may impose restrictions on that product, our collaborators or us, including requiring withdrawal of the product from the market. Our product candidates will also be subject to ongoing FDA and other foreign regulatory agency requirements for the labeling, packaging, storage, advertising, promotion, record-keeping and submission of safety and other post-market information on the drug. If our product candidates fail to comply with applicable regulatory requirements, a regulatory agency may:

- issue warning letters or other notices of possible violations,
- impose civil or criminal penalties or seek disgorgement of revenue or profits,
- suspend regulatory approval,
- suspend any ongoing clinical trials,

- refuse to approve pending applications or supplements to approved applications filed by us or our collaborators,
- impose restrictions on operations, including costly new manufacturing requirements, or
- seize or detain products or require a product recall.

In order to market any products outside of the U.S., we and our collaborators must establish and comply with numerous and varying regulatory requirements of other countries regarding safety and efficacy. Approval procedures vary among countries and can involve additional product testing and additional administrative review periods. The time required to obtain approval in other countries might differ from that required to obtain FDA approval. The regulatory approval process in other countries may include all of the risks regarding FDA approval in the U.S. Regulatory approval in one country does not ensure regulatory approval in another, but a failure or delay in obtaining regulatory approval in one country may negatively impact the regulatory process in others. Failure to obtain regulatory approval in other countries or any delay or setback in obtaining such approval could have the same adverse impact regarding FDA approval in the U.S., including the risk that our product candidates may not be approved for all indications requested, which could limit the uses of our product candidates and adversely impact potential royalties and product sales, and that such approval may be subject to limitations on the indicated uses for which the product may be marketed or require costly, post-marketing follow-up studies.

If we and our collaborators fail to comply with applicable foreign regulatory requirements, we and our collaborators may be subject to fines, suspension or withdrawal of regulatory approvals, product recalls, seizure of products, operating restrictions and criminal prosecution.

***If our competitors have products that are approved faster, marketed more effectively or demonstrated to be more effective than ours, our commercial opportunity will be reduced or eliminated.***

The biotechnology and biopharmaceutical industries are characterized by rapidly advancing technologies, intense competition and a strong emphasis on proprietary products. We face competition from many different sources, including commercial pharmaceutical and biotechnology enterprises, academic institutions, government agencies and private and public research institutions. Due to the high demand for treatments for liver and metabolic diseases, research is intense and new treatments are being sought out and developed by our competitors.

We are aware of many competitive products currently marketed or under development that are used to treat some of the diseases we have targeted. If CS-917 and/or MB07803 are ultimately determined safe and effective and approved for marketing, these products may compete for market share with established therapies from a number of competitors, including large pharmaceutical companies. Such marketed products include, but are not limited to the following classes:

- metformin a member of the biguanide drug class, related to guanidine and currently is the standard of care for type 2 diabetes,
- sulfonylureas increase the secretion of insulin by the pancreas, thereby lowering the level of the sugar glucose in the blood,
- insulins mimic the naturally occurring hormone insulin made by the pancreas to control blood glucose levels,
- peroxisome proliferator-activated receptor agonists (PPARs) - improve insulin sensitivity by activating certain genes involved in fat synthesis and carbohydrate metabolism,
- incretin mimetics mimic the naturally occurring hormone incretin, which reduces blood glucose levels by increasing the secretion of insulin from the pancreas, slowing absorption of glucose from the gut, and reducing the action of glucagon (glucagon is a hormone that increases glucose production by the liver),



- alpha-glucosidase inhibitors - decrease the absorption of carbohydrates from the intestine, resulting in a slower and lower rise in blood glucose throughout the day,
- glinides - stimulate the pancreas beta-cells to produce insulin, and
- combination therapies combines a member of any of the above-mentioned classes, particularly metformin, with a member from any of the other classes, for example, sulfonylureas or PPARs.

Metformin is a drug that, like CS-917 and MB07803, inhibits liver glucose production, albeit through an unknown mechanism. Because it does not cause weight gain, metformin is often prescribed as a first line therapy to obese diabetics, who are reported to comprise more than 90% of newly diagnosed type 2 diabetics. Generic forms of metformin have recently become available. Accordingly, unless CS-917 and MB07803 demonstrate significant benefits over metformin or demonstrate that they can be used in the patient population who do not tolerate and/or adequately respond to metformin treatment, the price required to effectively compete with the generic form of metformin may be so low that it becomes uneconomical for us or Daiichi Sankyo to market CS-917 and/or for us to market MB07803. Moreover, if the combination of CS-917 with metformin is contraindicated for safety reasons the market potential of CS-917 could be reduced and/or selling expenses could be increased. Should CS-917 eventually be approved and combination with metformin remains an issue, the FDA may require additional measures be taken during marketing, such as prominent warning labels known as black-box warnings, physician education programs and/or other steps to restrict concomitant use of CS-917 and metformin.

In addition, many companies are developing novel therapies that target diabetes. These companies may develop and introduce products competitive with or superior to CS-917 and/or MB07803.

If pradeфовir is ultimately determined safe and effective and approved for marketing, it may compete for market share with established therapies from a number of competitors, including large pharmaceutical companies. Such marketed products include, but are not limited to the following classes:

- interferons - mimic the naturally occurring interferon, an infection-fighting immune substance produced by the body,
- nucleoside analogues - chemically engineered nucleoside compounds that are converted inside cells into other compounds that are structurally similar to the building blocks of DNA and RNA that interfere with the replication of HBV, and
- nucleotide analogues - chemically engineered nucleotide compounds that are converted inside cells into other compounds that are structurally similar to the building blocks of DNA and RNA that interfere with the replication of HBV.

A competitor to pradeфовir may be Hepsera (adefovir dipivoxil), which is a nucleotide analogue currently marketed in the U.S. and Europe by Gilead Sciences, Inc. Pradeфовir and Hepsera are prodrugs of the same active drug, and therefore will directly compete. In order to effectively compete with Hepsera, pradeфовir may have to be significantly more beneficial or less expensive than Hepsera. In addition, marketed products approved to treat HIV infections are being evaluated for their effectiveness in treating hepatitis B infections.

There are no currently approved drugs for primary liver cancer. However, some companies are developing novel therapies specifically for primary liver cancer. In addition, companies are developing therapies for other solid tumors which may be efficacious in treating primary liver cancer. These companies may develop and introduce products competitive with or superior to MB07133.

If MB07811 is ultimately determined safe and effective and approved for marketing, it would compete with products marketed by several large pharmaceutical companies that currently comprise a large share of the hyperlipidemia market. Major classes of hyperlipidemia drugs include, but are not limited to:





- statins - reduce serum cholesterol levels by inhibiting a key enzyme involved in the biosynthesis of cholesterol,
- fibrates reduce the amount of cholesterol and triglycerides (fatty substances) in blood,
- nicotinic acid derivatives - lower cholesterol, triglycerides and low density lipoproteins and increase high density lipoproteins,
- cholesterol absorption inhibitors (CAIs) - inhibit the absorption of dietary and biliary cholesterol,
- bile acid sequestrants bind with cholesterol-containing bile acids in the intestines and remove them in bowel movements, and
- statin combination therapies - combine statins with members of the above-mentioned classes, particularly CAIs.

Several large pharmaceutical companies are also developing novel therapies that target hyperlipidemia. These companies may develop and introduce products competitive with or superior to MB07811. Lipitor (atorvastatin; a statin marketed by Pfizer Inc.) is currently the best selling prescription medicine. In addition, generic statins (cholesterol-reducers) have recently been approved in the major pharmaceutical markets, which would also compete with MB07811.

In addition, many other competitors are developing products for the treatment of the diseases we are targeting and if successful, these products could compete with our products. If we receive approval to market and sell any of our product candidates, we may compete with these companies and their products as well as others in varying stages of development.

Many of our competitors have significantly greater financial resources and expertise in research and development, manufacturing, preclinical testing, clinical trials, regulatory approvals and marketing approved products than we do. Smaller or early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. Our competitors may succeed in developing technologies and therapies that are more effective, better tolerated or less costly than any which we are developing, or that would render our product candidates obsolete and noncompetitive. Our competitors may succeed in obtaining approvals from the FDA and foreign regulatory authorities for their products sooner than we do for ours. We will also face competition from these third parties in recruiting and retaining qualified scientific and management personnel, establishing clinical trial sites and patient registration for clinical trials, and in acquiring and in-licensing technologies and products complementary to our programs or advantageous to our business.

***We do not have internal manufacturing capabilities, and if we fail to develop and maintain supply relationships with collaborators or other third-party manufacturers, we may be unable to develop or commercialize our products.***

Our ability to develop and commercialize our products depends in part on our ability to manufacture, or arrange for collaborators or other third parties to manufacture, our products at a competitive cost, in accordance with regulatory requirements and in sufficient quantities for clinical trials and eventual commercialization. Valeant and Daiichi Sankyo are currently responsible for all clinical and commercial manufacturing of pradefovir and CS-917, respectively. We have relied on a number of suppliers to manufacture sufficient quantities of MB07133, MB07803 and MB07811 for use in our current clinical trials. Although none of our current product candidates has been manufactured on a commercial scale our historical suppliers have manufactured other companies' products on a commercial scale. However, we have not yet determined if our suppliers are capable of manufacturing our products on a commercial scale. We, our collaborators and third-party manufacturers may encounter difficulties with the small- and large-scale formulation and manufacturing processes required to manufacture our product candidates, resulting in delays in our clinical trials and regulatory submissions, in the commercialization of our product candidates or, if any of our product candidates is approved, in the recall or withdrawal of the product from the market. Further, development of large-scale manufacturing processes may require additional validation studies,

which the FDA and other foreign regulatory agencies must review and approve. Our inability to enter into or maintain agreements with collaborators or capable third-party manufacturers on acceptable terms could delay or prevent the commercialization of our products, which would adversely affect our ability to generate revenues and could prevent us from achieving or maintaining profitability.

We currently expect that in any future clinical trials of MB07133, MB07803 and MB07811, we will rely on our current suppliers to manufacture these compounds. However, we do not have long-term supply agreements with these third parties, and we may not be able to enter into new supply agreements with them in a timely manner or on acceptable terms, if at all. These third parties may also be subject to capacity constraints that would cause them to limit the amount of these compounds that we can purchase. While we believe alternative sources to manufacture these compounds are readily available, in the event we have to seek such alternative sources we will incur costs associated with identifying and qualifying one or more alternate suppliers. In addition, any resulting interruption or delay we experience in the supply of MB07133, MB07803 or MB07811 may impede the clinical trials of these compounds.

In addition, we, our collaborators or other third-party manufacturers of our products must comply with current good manufacturing practices, or CGMP, requirements enforced by the FDA and other foreign regulatory agencies through their facilities inspection programs. These requirements include quality control, quality assurance and the maintenance of records and documentation. In addition, product manufacturing facilities in California are subject to licensing requirements of the California Department of Health Services and may be inspected by the California Department of Health Services, and other applicable regulatory authorities, at any time. We, our collaborators or other third-party manufacturers of our products may be unable to comply with these CGMP requirements and with other FDA, state and foreign regulatory requirements. We have little control over third-party manufacturers' compliance with these regulations and standards. A failure to comply with these requirements may result in fines and civil penalties, suspension of production, suspension or delay in product approval, product seizure or recall, or withdrawal of product approval.

***If we are unable to establish sales and marketing capabilities or enter into agreements with third parties to sell and market our product candidates, we may be unable to generate significant revenues.***

We do not have a sales and marketing organization, and we have no experience as a company in the sales, marketing and distribution of pharmaceutical products. Valeant and Daiichi Sankyo are currently responsible for worldwide marketing and commercialization for pradefovir and CS-917, respectively, although we have an option to co-promote CS-917 in North America with Daiichi Sankyo. Although our hepatitis C and metabolic disease collaborations with Merck have not yet yielded product candidates, should they be successful, Merck will be responsible for worldwide marketing and commercialization of any resulting product candidates (subject to, in the case of our metabolic disease collaboration, our option to co-promote the product in the U.S. with certain financial assistance from Merck). Similarly, should our hepatitis C collaboration with Idenix be successful, Idenix will be responsible for worldwide marketing and commercialization of any resulting product candidates. In order to co-promote any of these products, or to commercialize MB07133, MB07803, MB07811 or any future product candidates, we must develop our sales, marketing and distribution capabilities, or make arrangements with a third party to perform these services. Even though we may receive financial assistance from Merck if we exercise our co-promotion option under the metabolic disease collaboration developing a sales force for any resulting product or any product resulting from any of our other product candidates is expensive, and time consuming and could delay any product launch. We may be unable to establish and manage an effective sales force in a timely or cost-effective manner, if at all, and any sales force we do establish may not be capable of generating sufficient demand for our product candidates. To the extent that we enter into arrangements with collaborators or other third parties to perform sales and marketing services, our product revenues are likely to be lower than if we directly marketed and sold our product candidates. If we are unable to establish adequate sales and marketing capabilities, independently or with others, we may not be able to generate significant revenues and may not become profitable.

***The commercial success of our product candidates depends upon their market acceptance among physicians, patients, healthcare payors and the medical community.***

Even if our product candidates obtain regulatory approval, our products, if any, may not gain market acceptance among physicians, patients, healthcare payors and the medical community. The degree of market acceptance of any of our approved product candidates will depend on a number of factors, including:

- our ability to provide acceptable evidence of safety and efficacy,
- relative convenience and ease of administration,
- the prevalence and severity of any adverse side effects,
- restrictions on use in combination with other products,
- availability of alternative treatments,
- pricing and cost effectiveness,
- effectiveness of our or our partners' sales and marketing strategy, and
- our ability to obtain sufficient third-party coverage or reimbursement.

If approved, CS-917 may have to be administered several times daily. Additionally, it may result in variable drug levels in different patient populations, which could complicate its use and limit its marketability. Since CS-917 is eliminated from the body through the kidney, it may be of limited use in diabetics with kidney dysfunction. In addition, CS-917 and HepDirect prodrugs such as pradeфовir and MB07133 may also exhibit interactions with other marketed drugs that could limit their combination with those drugs. Serious adverse events observed in early 2005 in a Phase 1 clinical trial of CS-917 in combination with metformin have raised questions about the safety of the potential use of CS-917 and metformin in combination. Therefore, even if CS-917 receives regulatory approval, its combination with metformin may be restricted which may reduce its market potential. In addition, various risk management strategies may be required to minimize inadvertent use with metformin including prominent warning labels known as "black-box" warnings, physician education programs and/or other steps designed to more tightly control the sale and use of CS-917. Such strategies and programs, if required, will likely adversely impact the sales of CS-917 and may incur additional selling expenses thereby reducing profits. In addition, primarily because the number of treatable patients in the U.S. with primary liver cancer is relatively small, we expect to market MB07133, if approved, at a relatively high price in the U.S. in order to generate sufficient revenues to recoup our costs and provide a return on our investment. This could limit or prevent us from achieving the market acceptance of MB07133 in the U.S. The number of treatable patients outside of the U.S. is much larger than the number of treatable patients in the U.S. However, because third party reimbursement in many of these countries is uncertain, we may be unable to recoup our costs or generate sufficient returns on our investment in these countries. If any of our product candidates is approved but does not achieve an adequate level of acceptance by physicians, healthcare payors and patients, we may not generate sufficient revenue from this product candidate and we may not become or remain profitable.

***We are subject to uncertainty relating to health care reform measures and reimbursement policies which, if not favorable to our product candidates, could hinder or prevent our product candidates' commercial success.***

The continuing efforts of the government, insurance companies, managed care organizations and other payers of health care costs to contain or reduce costs of health care may adversely affect:

- our ability to set a price we believe is fair for our products,
- our ability to generate revenues and achieve or maintain profitability,
- the future revenues and profitability of our potential customers, suppliers and collaborators, and

- the availability of capital.

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In certain foreign markets, the pricing of prescription drugs is subject to government control. In the U.S., given recent federal and state government initiatives directed at lowering the total cost of health care, Congress and state legislatures will likely continue to focus on health care reform, the cost of prescription drugs and the reform of the Medicare and Medicaid systems. For example, the Medicare Prescription Drug, Improvement and Modernization Act of 2003 provides a new Medicare prescription drug benefit that began in 2006 and mandates other reforms. While we cannot predict the full outcome of the implementation of this legislation, it is possible that the new Medicare prescription drug benefit, which will be managed by private health insurers and other managed care organizations, will result in decreased reimbursement for prescription drugs, which may further exacerbate industry-wide pressure to reduce prescription drug prices. This could harm our ability to market our products and generate revenues. It is also possible that other similar proposals will be adopted.

Our ability to commercialize our product candidates successfully will depend in part on the extent to which governmental authorities, private health insurers and other organizations establish appropriate coverage and reimbursement levels for the cost of our products and related treatments. Third-party payors including state governments are increasingly challenging the prices charged for medical products and services. Also, the trend toward managed health care in the U.S., which could significantly influence the purchase of health care services and products, as well as legislative proposals to reform health care or reduce government insurance programs, may result in lower prices for our product candidates or exclusion of our product candidates from coverage and reimbursement programs. The cost containment measures that health care payors and providers are instituting and the effect of any health care reform could significantly reduce our revenues from the sale of any approved product.

***We will need to increase the size of our organization, and we may experience difficulties in managing growth.***

Since we became an independent company in 1999, we have increased the number of our full-time employees from 50 to 114 as of September 30, 2006. We may need to continue to expand our managerial, operational, financial and other resources in order to manage and fund our operations and clinical trials, continue our research and development and collaborative activities, and commercialize our product candidates. It is possible that our management and scientific 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 various projects requires that we continue to improve our operational, financial and management controls, reporting systems and procedures 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 and commercialization goals.

***If we fail to attract and keep key management and scientific personnel, we may be unable to successfully develop or commercialize our product candidates.***

Our success depends on our continued ability to attract, retain and motivate highly qualified management and scientific personnel. The loss of the services of certain principal members of our management or scientific staff could delay or prevent the commercialization of our product candidates. We employ these individuals on an at-will basis and their employment can be terminated by us or them at any time, for any reason and with or without notice, subject to the terms of their stock restriction agreements and severance agreements.

Competition for qualified personnel in the biotechnology field is intense. We will need to hire additional personnel as we establish and/or expand our sales, manufacturing, research and development activities in the future. We may not be able to attract and retain quality personnel on acceptable terms given the competition for such personnel among biotechnology, pharmaceutical and other companies.

We have established a scientific advisory board, the members of which assist us in formulating our research, development and clinical strategies. These scientific advisors are not our employees and may have commitments to, or consulting or advisory contracts with, other entities that may limit their availability to us. In addition, our scientific advisors may have arrangements with other companies to assist those companies in developing products or technologies that may compete with ours.

*We have limited experience in identifying, completing and integrating acquisition targets, and if we do not successfully integrate any future acquisitions, we may incur unexpected costs and disruptions to our business.*

An important part of our business strategy is to continue to develop a broad pipeline of product candidates. In addition to our internal drug development efforts, we may seek to expand our product pipeline, at the appropriate time and as resources allow, by acquiring products or businesses or in-licensing technologies that we believe are a strategic fit with our business and complement our existing product candidates and research programs. Future acquisitions, however, may entail numerous operational and financial risks including:

- exposure to unknown liabilities,
- disruption of our business and diversion of our management's time and attention to developing acquired products or technologies,
- incurrence of substantial debt or dilutive issuances of securities to pay for acquisitions,
- higher than expected acquisition and integration costs,
- increased amortization expenses,
- difficulty and cost in combining the operations and personnel of any acquired businesses with our operations and personnel,
- impairment of relationships with key suppliers or customers of any acquired businesses due to changes in management and ownership, and
- inability to retain key employees of any acquired businesses.

We have limited experience in identifying acquisition targets, successfully completing potential acquisitions and integrating any acquired products, businesses or technologies into our current infrastructure. Moreover, we may devote resources to potential acquisitions that are never completed or fail to realize the anticipated benefits of any acquisition.

#### **Risks Related to our Finances and Capital Requirements**

*We have a history of net losses, which we expect to continue for the foreseeable future, and we are unable to predict the extent of future losses or when we will become profitable, if ever.*

We have incurred net losses from our inception. As of September 30, 2006, we had an accumulated deficit of approximately \$98.5 million. We expect to increase our operating expenses over the next several years as we continue and expand our research and development activities, including conducting clinical trials for our product candidates and further developing our product pipeline, acquiring or in-licensing products, technologies or businesses, and funding other working capital and general corporate purposes. As a result, we expect to continue to incur significant and increasing operating losses for the foreseeable future. Because of the numerous risks and uncertainties associated with our product development efforts, we are unable to predict the extent of any future losses or when we will become profitable, if ever.

*We currently lack a significant continuing revenue source and may not become or remain profitable.*

Our ability to become and remain profitable depends upon our ability to generate continuing revenues. To date, our product candidates and strategic collaborations have not generated any significant revenues, other than one-time or time-limited payments associated with our collaborations such as milestone payments and option fees. Our ability to generate significant continuing revenues depends on a number of factors, including:

- successful completion of ongoing clinical trials for our product candidates,





- achievement of regulatory approval for our product candidates,
- successful completion of our current and future strategic collaborations, and
- successful sales, manufacturing, distribution and marketing of our products.

We do not anticipate that we will generate significant continuing revenues for several years. If we are unable to eventually generate significant continuing revenues, we will not become or remain profitable, and we may be unable to continue our operations.

*We will need substantial additional funding and may be unable to raise capital when needed, which would force us to delay, reduce or eliminate our research and development programs or commercialization efforts and affect our ability to continue as a going concern.*

We believe that our existing cash, cash equivalents and short-term investments will be sufficient to meet our projected operating requirements through at least the next twelve months. Because we do not anticipate that we will generate significant continuing revenues for several years, if at all, we will need to raise substantial additional capital to finance our operations in the future. Our additional funding requirements will depend on, and could increase significantly as a result of, many factors, including:

- the rate of progress and cost of our clinical trials and other research and development activities,
- the scope, prioritization and number of clinical development and research programs we pursue,
- the costs of expanding our operations,
- the terms and timing of any collaborative, licensing and other arrangements that we may establish,
- the costs of filing, prosecuting, defending and enforcing any patent claims and other intellectual property rights,
- the costs and timing of regulatory approvals,
- the costs of establishing or contracting for sales and marketing capabilities,
- the effect of competing technological and market developments, and
- the extent to which we acquire or in-license new products, technologies or businesses.

Until we can generate significant continuing revenues, if ever, we expect to satisfy our future cash needs through public or private equity offerings, debt financings, grants or corporate collaboration and licensing arrangements, as well as through interest income earned on cash balances.

We cannot be certain that additional funding will be available on acceptable terms, or at all. If adequate funds are not available, we may be required to delay, reduce the scope of or eliminate one or more of our research and development programs or our commercialization efforts and we may be unable to continue as a going concern.

*Raising additional funds by issuing securities or through collaboration and licensing arrangements will cause dilution to existing stockholders, restrict our operations or require us to relinquish proprietary rights.*

We may raise additional funds through public or private equity offerings, the CEFF, debt financings, grants or corporate collaboration and licensing arrangements. For example, we have an effective shelf registration statement on file with the Securities and Exchange Commission which allows us to issue shares of our common stock and warrants to purchase our common stock for an aggregate initial offering price of up to \$75 million. To



date, we have sold approximately \$40 million of our common stock under this registration statement. Under the terms of the CEFF, we have agreed to file a registration statement with the Securities and Exchange Commission covering the resale of shares issuable under this agreement. We may sell additional securities from time to time in one or more offerings in amounts, at prices and on terms that we will determine at the time of the offering. To the extent that we raise additional capital by issuing equity securities, pursuant to our effective shelf registration statement or otherwise, our existing stockholders' ownership will be diluted.

Any debt financing we enter into may involve covenants that restrict our operations. These restrictive covenants may include limitations on additional borrowing, specific restrictions on the use of our assets as well as prohibitions on our ability to create liens, pay dividends, redeem our stock or make investments. In addition, if we raise additional funds through collaboration and licensing arrangements, it may be necessary to relinquish potentially valuable rights to our potential products or proprietary technologies, or grant licenses on terms that are not favorable to us.

***Our quarterly operating results and stock price may fluctuate significantly.***

We expect our operating results to be subject to quarterly fluctuations. The revenues we generate, if any, and our operating results will be affected by numerous factors, including:

- the development status of our product candidates, including results of our clinical trials,
- our recommendation of additional drug compounds for clinical development,
- our addition or termination of research programs or funding support,
- variations in the level of expenses related to our product candidates or research programs,
- our execution of collaborative, licensing or other arrangements, and the timing of payments we may make or receive under these arrangements, and
- changes in the use assumptions or the use of different valuation methods in the application of SFAS No. 123R in future periods.

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.

**Risks Related to our Intellectual Property**

***Our success depends upon our ability to protect our intellectual property, including the proprietary technologies and compounds used in our business.***

Our commercial success depends on obtaining and maintaining patent protection and/or trade secret protection of our product candidates, proprietary technologies and their uses, as well as successfully defending any patents that issue against third-party challenges. We may only be able to protect our product candidates, proprietary technologies and their uses from unauthorized use by third parties to the extent that valid and enforceable patents or trade secrets cover them.

The filing, prosecution and defense of patents at pharmaceutical and biotechnology companies can be highly uncertain and involve complex legal and factual questions for which important legal principles remain unresolved. No consistent policy regarding the breadth of claims allowed in biotechnology patents has emerged to date in the U.S. The biotechnology patent situation outside the U.S. is even more uncertain. We may be particularly affected by this because we expect that pradefovir and MB07133, if approved, will be marketed in foreign countries with high incidences of HBV and primary liver cancer, respectively. Decisions or actions regarding patent filing

and/or changes in either the patent laws or in interpretations of patent laws in the U.S. and other countries may diminish the value of our intellectual property.

Decisions or actions regarding patent filing are complex and we may not be successful in protecting our products from competition. Patent positions for products are highly uncertain and involve complex legal and factual questions which may ultimately be decided to the detriment of our products competitive positions in the U.S. and these other countries. We may not be able to develop patentable products or processes in the U.S. and these other countries, and may not be able to obtain patents from pending applications. Even if patent claims are allowed in the U.S. and these other countries, the claims may not issue, or in the event of issuance, may not be sufficient to protect the technology owned by or licensed to us. Any patents or patent rights that we obtain in the U.S. and other countries may be circumvented, challenged or invalidated by our competitors. In addition, we are dependent on outside patent firms for advice and action regarding our efforts to secure patents. Should these firms fail to take appropriate action to secure or enforce our patents in a timely manner, or should they provide us with incorrect or inappropriate advice it could be detrimental to our patent positions.

Accordingly, we cannot predict the breadth of claims that may be allowed or enforced in our patents or in third-party patents in the U.S. and other countries.

The degree of future protection for our proprietary rights is uncertain because legal means afford only limited protection and may not adequately protect our rights or permit us to gain or keep our competitive advantage. For example:

- we might not have been the first to make the inventions covered by each of our pending patent applications and issued patents,
- we might not have been the first to file patent applications for these inventions,
- others may independently develop similar or alternative technologies or duplicate any of our technologies,
- it is possible that none of our pending patent applications will result in issued patents,
- our issued patents may not provide a basis for commercially viable products, may not provide us with any competitive advantages, or may be challenged by third parties,
- our issued patents may not be valid or enforceable,
- we may not develop additional proprietary technologies that are patentable, or
- the patents of others may have an adverse effect on our business.

Proprietary trade secrets and unpatented know-how are also very important to our business. Although we have taken steps to protect our trade secrets and unpatented know-how, including entering into proprietary information and inventions agreements with our employees and consultants and entering into confidentiality agreements with other third parties to whom we disclose our proprietary information, third parties may still obtain this information without our knowledge and consent. Enforcing a claim that a third party illegally obtained and is using our trade secrets or unpatented know-how is expensive and time consuming, and the outcome is unpredictable. In addition, courts outside the U.S. may be less willing to protect this information. Moreover, our competitors may independently develop equivalent knowledge, methods and know-how.

***If we are sued for infringing intellectual property rights of third parties, it will be costly and time consuming, and an unfavorable outcome in that litigation would have a material adverse effect on our business.***

Our commercial success depends upon our ability and the ability of our collaborators to develop, manufacture, market and sell our product candidates and use our proprietary technologies without infringing the



proprietary rights of third parties. Numerous U.S. and foreign issued patents and pending patent applications, which are owned by third parties, exist in the fields in which we and our collaborators are developing products. Because patent applications can take many years to issue, there may be currently pending applications, unknown to us, which may later result in issued patents that our product candidates or proprietary technologies may infringe. We have not conducted a complete search of existing patents to identify existing patents that our product candidates or proprietary technologies may inadvertently infringe.

We may be exposed to future litigation by the companies holding these patents or other third parties based on claims that our product candidates and/or proprietary technologies infringe their intellectual property rights. If one of these patents was found to cover our product candidates, proprietary technologies or their uses, we or our collaborators could be required to pay damages and could be unable to commercialize our product candidates or use our proprietary technologies unless we or they obtained a license to the patent. In addition, while we are not currently subject to pending litigation nor are we aware of any threatened litigation, third parties may contact us or our collaborators in the ordinary course of business to bring certain patents to our attention. We and our collaborators evaluate all such communications on a case-by-case basis to assess whether such patents cover our product candidates or proprietary technologies and if so, whether to seek a license from such third parties. A license may not be available to us or our collaborators on acceptable terms, if at all.

There is a substantial amount of litigation involving patent and other intellectual property rights in the biotechnology and biopharmaceutical industries generally. If a third party claims that we or our collaborators infringe on its technology, we may face a number of issues, including:

- infringement and other intellectual property claims which, with or without merit, may be expensive and time-consuming to litigate and may divert our management's attention from our core business,
- substantial damages for infringement, including treble damages and attorneys' fees, as well as damages for products developed using allegedly infringing drug discovery tools or methods, which we may have to pay if a court decides that the product or proprietary technology at issue infringes on or violates the third party's rights,
- a court prohibiting us from selling or licensing the product or using the proprietary technology unless the third party licenses its technology to us, which it is not required to do,
- if a license is available from the third party, we may have to pay substantial royalties, fees and/or grant cross licenses to our technology, and
- redesigning our products or processes so they do not infringe, which may not be possible or may require substantial funds and time.

We have conducted searches of U.S. and foreign patents, but cannot guarantee that the searches were comprehensive and therefore whether any of our product candidates or the methods of using, making or identifying our product candidates infringe the patents searched, or that other patents do not exist that cover our product candidates or these methods. There may also be pending patent applications that are unknown to us and may prevent us from marketing our product candidates. Other product candidates that we may develop, either internally or in collaboration with others, could be subject to similar delays and uncertainties.

***Existing patents and patent applications covering adefovir or prodrugs of adefovir in the U.S. and foreign countries may prevent the commercialization of pradefovir in the future.***

Our product candidate pradefovir is a prodrug of adefovir. A third party, Gilead, has rights to another product called Hepsara that is a non-liver specific prodrug of adefovir. We are aware of third party patents and patent applications in the U.S. and in European and other foreign countries with claims to prodrugs of adefovir. These patents are scheduled to expire in September 2011 overseas and in 2014 in the U.S. Although we do not believe that any valid claim covers pradefovir, we cannot guarantee this. If it is determined that patent claims are valid and cover pradefovir, we may not be able to commercialize pradefovir in such countries, including those in

Europe. Further, we are aware that a patent term extension of one of these prodrug patents has been granted in multiple European countries based on the regulatory approval of Hepsera thereby extending protection of Hepsera in those countries to September 2016. Additional third party patents covering Hepsera or adefovir may exist, and may expire later than our expected date of regulatory approval in the country where the patent is in force.

#### **Risks Related to Other Legal Matters**

*We may incur significant costs complying with environmental laws and regulations.*

We use hazardous materials, including chemicals, biological agents and radioactive isotopes and compounds that could be dangerous to human health and safety or the environment. As appropriate, we store these materials and wastes resulting from their use at our facility pending their ultimate use or disposal. We currently contract with a third party to dispose of these materials and wastes. We are subject to a variety of federal, state and local laws and regulations governing the use, generation, manufacture, storage, handling and disposal of these materials and wastes. We may also incur significant costs complying with environmental laws and regulations adopted in the future.

*We may incur substantial liabilities from any product liability claims if our insurance coverage for those claims is inadequate.*

We face an inherent risk of product liability exposure related to the testing of our product candidates in human clinical trials, and will face an even greater risk if we sell our product candidates commercially. For example, in March 2005 two cases of lactic acidosis were observed in a clinical trial combining CS-917 with metformin. As a result, unless further data changes the situation, the combination of CS-917 and metformin is contraindicated and the inadvertent combination of the drugs could put patients at risk for lactic acidosis. Therefore, even if CS-917 receives regulatory approval the FDA may require that additional measures be taken during marketing, such as prominent warning labels known as "black-box" warnings, physician education programs and/or other steps to restrict concomitant use of metformin and CS-917. However, none of these programs can be assured of eliminating the possibility of the inadvertent use of CS-917 with metformin and the consequent risk of lactic acidosis. Therefore, these programs may not effectively protect us from a liability claim.

An individual may bring a liability claim against us if one of our product candidates causes, or merely appears to have caused, an injury. If we cannot successfully defend ourselves against the product liability claim, we will incur substantial liabilities. Regardless of merit or eventual outcome, liability claims may result in:

- decreased demand for our product candidates,
- injury to our reputation,
- withdrawal of clinical trial participants,
- costs of related litigation,
- substantial monetary awards to patients or other claimants,
- loss of revenues, and
- the inability to commercialize our product candidates.

We have product liability insurance that covers our clinical trials, up to an annual aggregate limit of \$10 million. We intend to expand our insurance coverage to include the sale of commercial products if marketing approval is obtained for any of our product candidates. However, insurance coverage is increasingly expensive. We may not be able to maintain insurance coverage at a reasonable cost and we may not be able to obtain insurance coverage that will be adequate to satisfy any liability that may arise.

*If we use biological and hazardous materials in a manner that causes injury, we may be liable for damages.*

Our research and development and manufacturing activities involve the use of biological and hazardous materials. Although we believe our safety procedures for handling and disposing of these materials comply with federal, state and local laws and regulations, we cannot entirely eliminate the risk of accidental injury or contamination from the use, storage, handling or disposal of these materials. If one of our employees was accidentally injured from the use, storage, handling or disposal of these materials, the medical costs related to his or her treatment would be covered by our workers' compensation insurance policy. While our property and casualty and general liability insurance policies specifically exclude coverage for damages and fines arising from biological or hazardous waste exposure or contamination, we do carry separate pollution legal liability coverage that is intended to cover third party claims for bodily injury, property damage and remediation costs. However, in the event of contamination or injury, we could be held liable for damages or penalized with fines in an amount exceeding our insurance and/or resources.

#### **Risks Related to the Securities Markets and Investment in our Common Stock**

*Market volatility may affect our stock price and the value of your investment.*

The market price for our common stock has been and is likely to continue to be volatile. In addition, the market price of our common stock may fluctuate significantly in response to a number of factors, most of which we cannot control, including:

- changes in the regulatory status of our product candidates, including the status and results of our clinical trials,
- events affecting Valeant, Daiichi Sankyo, Merck or any future collaborators,
- announcements of new products or technologies, commercial relationships or other events by us or our competitors,
- regulatory developments in the U.S. and foreign countries,
- fluctuations in stock market prices and trading volumes of similar companies,
- variations in our quarterly operating results,
- changes in securities analysts' estimates of our financial performance,
- changes in accounting principles,
- issuances of new equity securities by us, pursuant to our effective shelf registration statement or otherwise,
- sales of large blocks of our common stock, including sales by our executive officers, directors and significant stockholders,
- additions or departures of key personnel, and
- discussion of us or our stock price by the financial and scientific press and in online investor communities.



***Anti-takeover provisions in our 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 amended and restated certificate of incorporation and bylaws may delay or prevent an acquisition of us or a change in our management. These provisions include a classified board of directors, a prohibition on actions by written consent of our stockholders, and the ability of our board of directors to issue preferred stock without stockholder approval. In addition, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporation Law, which prohibits stockholders owning in excess of 15% of our outstanding voting stock from merging or combining with us. Although we believe these provisions collectively provide for an opportunity to receive higher bids by requiring potential acquirers to negotiate with our board of directors, they would apply even if the offer may be considered beneficial by some stockholders. In addition, 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, which is responsible for appointing the members of our management.

***We may incur increased costs as a result of changes in laws and regulations relating to corporate governance matters.***

Changes in the laws and regulations affecting public companies, including the provisions of the Sarbanes-Oxley Act of 2002 and rules adopted or proposed by the Securities and Exchange Commission and by the Nasdaq Stock Market, will result in increased costs to us as we continue to evaluate the implications of these laws and regulations and respond to their requirements. These laws and regulations could make it more difficult or more costly for us to obtain certain types of insurance, including director and officer liability insurance, and we may be forced to accept reduced policy limits and coverage or incur substantially higher costs to obtain the same or similar coverage. The impact of these events could also make it more difficult for us to attract and retain qualified persons to serve on our board of directors, our board committees or as executive officers. We are presently evaluating and monitoring developments with respect to these laws and regulations and cannot predict or estimate the amount or timing of additional costs we may incur to respond to their requirements.

***Investor confidence and share value may be adversely impacted if our independent auditors are unable to provide us with the attestation of the adequacy of our internal controls over financial reporting, as required by Section 404 of the Sarbanes-Oxley Act of 2002.***

Beginning with our annual report on Form 10-K for the fiscal year ending December 31, 2006, we will be required pursuant to Section 404 of the Sarbanes-Oxley Act of 2002 to include in our annual reports on Form 10-K an assessment by our management of the effectiveness of our internal controls over financial reporting. In addition, our independent auditors must attest to and report on our management's assessment. How companies are implementing these requirements including internal control reforms, if any, and how independent auditors are applying these requirements and testing internal controls, remain subject to some uncertainty. In addition, any control system, regardless of how well designed, operated and evaluated, can provide only reasonable, not absolute, assurance that its objectives will be met. If, during any year, our independent auditors are not satisfied with our internal controls over financial reporting or the level at which these controls are documented, designed, operated, tested or assessed, or if our independent auditors interpret the applicable requirements, rules or regulations differently than we do, then they may decline to attest to management's assessment or may issue a report that is qualified. This could result in an adverse reaction in the financial marketplace due to a loss of investor confidence in the reliability of our financial statements, which could negatively impact the market price of our common stock.

***If our executive officers, directors and largest stockholders choose to act together, they may be able to control our operations and act in a manner that advances their best interests and not necessarily those of other stockholders.***

Our executive officers, directors and holders of 5% or more of our outstanding common stock, beneficially owned approximately 67% of our common stock as of September 30, 2006. As a result, these stockholders, acting together, are able to control all matters requiring approval by our stockholders, including the election of directors and the approval of mergers or other business combination transactions. The interests of this group of stockholders may not always coincide with our interests or the interests of other stockholders, and they may act in a manner that advances their best interests and not necessarily those of other stockholders.

*Future sales of our common stock may cause our stock price to decline.*

A large portion of our shares are held by a small number of persons and investment funds. In addition, these persons and funds hold warrants to purchase 4,057,176 shares of common stock that, if exercised, will result in these additional shares becoming available for sale. Moreover, several of our stockholders and warrant holders have rights, subject to some conditions, to require us to file registration statements covering the unregistered shares they currently hold or may acquire upon exercise of warrants, or to include these shares in registration statements that we may file for ourselves or other stockholders. Recently, we entered into a CEFF agreement with Kingsbridge under the terms of which it is committed to purchase up to \$50 million of our common stock over a 36 month period. Sales by these current and potential future stockholders or warrant holders of a substantial number of shares could significantly reduce the market price of our common stock.

**Risks Related to our Committed Equity Financing Facility**

*Our committed equity financing facility with Kingsbridge may not be available to us if we elect to make a draw down, may require us to make additional blackout or other payments to Kingsbridge and may result in dilution to our stockholders.*

In November 2006, we entered into the CEFF with Kingsbridge. The CEFF entitles us to sell and obligates Kingsbridge to purchase, from time to time over a period of 36 months, shares of our common stock for cash consideration up to an aggregate of \$50.0 million, subject to specified conditions and restrictions. Kingsbridge will not be obligated to purchase shares under the CEFF unless specified conditions are met, which include a minimum price for our common stock; the accuracy of representations and warranties made to Kingsbridge; compliance with laws; and the effectiveness of a registration statement registering for resale the shares of common stock to be issued in connection with the CEFF. In addition, among other termination rights, Kingsbridge is permitted to terminate the CEFF by providing written notice to us within 10 business days after it obtains actual knowledge that an event has occurred resulting in a material and adverse effect on our business, operations, properties or financial condition (subject to specified exceptions, including conditions or events that are reasonably expected to occur in the ordinary course of our business). If we are unable to access funds through the CEFF, or if Kingsbridge terminates the CEFF, we may be unable to access capital on favorable terms, or at all.

We are entitled, in certain circumstances, to deliver a blackout notice to Kingsbridge to suspend the use of this prospectus and prohibit Kingsbridge from selling shares under this prospectus for a certain period of time. If we deliver a blackout notice in the 15 trading days following the settlement of a draw down, or if the registration statement of which this prospectus is a part is not effective in circumstances not permitted by our registration rights agreement with Kingsbridge, then we must make a payment to Kingsbridge, or issue Kingsbridge additional shares in lieu of this payment, calculated on the basis of a specified number of shares held by Kingsbridge immediately prior to the blackout period and the change in the market price of our common stock during the period in which the use of the registration statement is suspended. If the trading price of our common stock declines during a suspension of the resale registration statement, the blackout or other payment could be significant.

Should we sell shares to Kingsbridge under the CEFF, or issue shares in lieu of a blackout payment, it will have a dilutive effect on the holdings of our current stockholders and may result in downward pressure on the price of our common stock. If we draw down amounts under the CEFF, we will issue shares to Kingsbridge at a discount of up to 10% from the volume weighted average price of our common stock. If we draw down amounts under the CEFF when our stock price is decreasing, we will need to issue more shares to raise the same amount than if our stock price was higher. Issuances in the face of a declining stock price will have an even greater dilutive effect than if our stock price were stable or increasing and may further decrease our stock price.

## **FORWARD-LOOKING STATEMENTS**

This prospectus and the documents incorporated herein by reference contain forward-looking statements within the meaning of Section 27A of the Securities Act, and Section 21E of the Securities Exchange Act of 1934, as amended, or the Exchange Act, regarding, among other things, our business, our financial position and the research and development of biopharmaceutical products. Forward-looking statements include all statements that are not historical facts and can be identified by terms such as anticipates, believes, could, estimates, expects, intends, may, potential, predicts, projects, should, will, would or similar expressions. Such statements are based largely upon our expectations and projections about future events, and so are subject to certain risks and uncertainties, particularly those inherent in the process of developing and commercializing biopharmaceutical products, that could cause actual results to differ materially from those expressed in or implied by the forward-looking statements. Among the factors that could cause actual results to differ materially from those expressed in or implied by the forward-looking statements are risks and uncertainties incorporated by reference under Risk Factors in this prospectus and in our other filings with the SEC.

Although our forward-looking statements reflect good faith beliefs of our management, these statements are based only on facts and circumstances currently known to us. As a result, we cannot guarantee future results, events, levels of activity, performance or achievement as expressed in or implied by our forward-looking statements. We undertake no obligation to publicly update or revise any forward-looking statements, whether as a result of new information, future events or otherwise, unless required by law.

## **USE OF PROCEEDS**

We will not receive any of the proceeds from the sale of shares of our common stock by the selling stockholder pursuant to this prospectus. Any sale of shares by us to Kingsbridge under the common stock purchase agreement or in connection with the exercise of the Kingsbridge warrant will be made pursuant to an exemption from the registration requirements of the Securities Act. We will use the proceeds from these sales of shares to Kingsbridge for general corporate purposes, clinical trials, research and development expenses, general and administrative expenses, manufacturing expenses, and potential acquisitions of companies and technologies that complement our business, although we are not currently a party to any binding agreements or commitments with respect to the acquisition of any companies or technologies. As of the date of this prospectus, we cannot specify with certainty all of the particular uses for the net proceeds to us from the sale of shares to Kingsbridge. Accordingly, we will retain broad discretion over the use of these proceeds, if any.

### SELLING STOCKHOLDER

This prospectus relates to the possible resale by Kingsbridge of shares of common stock that we may issue pursuant to the common stock purchase agreement we entered into with Kingsbridge on November 2, 2006, or upon exercise of the warrant that we issued to Kingsbridge on November 2, 2006. We are filing the registration statement of which this prospectus is a part pursuant to the provisions of the registration rights agreement we entered into with Kingsbridge on November 2, 2006.

The selling stockholder may from time to time offer and sell pursuant to this prospectus any or all of the shares that it acquires under the common stock purchase agreement or upon exercise of the warrant.

The following table presents information regarding Kingsbridge, as the selling stockholder, and the shares that it may offer and sell from time to time under this prospectus. This table is prepared based on information supplied to us by the selling stockholder, and reflects holdings as of November 3, 2006. As used in this prospectus, the term "selling stockholder" includes Kingsbridge and any donees, pledges, transferees or other successors in interest selling shares received after the date of this prospectus from a selling stockholder as a gift, pledge, or other non-sale related transfer. The number of shares in the column "Number of Shares Being Offered" represents all of the shares that a selling stockholder may offer under this prospectus. The selling stockholder may sell some, all or none of its shares. We do not know how long the selling stockholder will hold the shares before selling them, and we currently have no agreements, arrangements or understandings with the selling stockholder regarding the sale of any of the shares.

Beneficial ownership is determined in accordance with Rule 13d-3(d) promulgated by the SEC under the Exchange Act. The percentage of shares of common stock beneficially owned prior to the offering shown in the table below is based both on an aggregate of 30,384,278 shares of our common stock outstanding on November 3, 2006, and on the assumption that all shares of common stock issuable under the common stock purchase agreement with Kingsbridge and all shares of common stock issuable upon exercise of the warrant by Kingsbridge are outstanding as of that date.

Stockholders	Shares of Common Stock Beneficially Owned Prior to Offering		Number of Shares Being Offered	Shares of Common Stock Beneficially Owned After Offering		
	Number	Percent		Number	Percent	
Kingsbridge Capital Limited(1)	6,046,471	(2)	16.6	% 6,046,471	0	*%

\* Less than one percent.

- (1) The business address of Kingsbridge Capital Limited is PO Box 1075, Elizabeth House, 9 Castle Street, St. Helier, Jersey, JE42QP, Channel Islands.
- (2) Consists of 6,046,471 shares of common stock, the maximum number of shares of common stock issuable under the committed equity financing facility we entered into with Kingsbridge on November 2, 2006, including 260,000 shares of common stock issuable upon exercise of the warrant we issued to Kingsbridge on November 2, 2006, which warrant is not exercisable before May 2, 2007. For the purposes hereof, we assume the issuance of all 6,046,471 shares. Adam Gurney and Maria O'Donoghue have shared voting and investment control of the securities held by Kingsbridge.

### PLAN OF DISTRIBUTION

We are registering 6,046,471 shares of common stock under this prospectus on behalf of Kingsbridge. Except as described below, to our knowledge, the selling stockholder has not entered into any agreement, arrangement or understanding with any particular broker or market maker with respect to the shares of common stock offered hereby, nor, except as described below, do we know the identity of the brokers or market makers that will participate in the sale of the shares.

The selling stockholder may decide not to sell any shares. The selling stockholder may from time to time offer some or all of the shares of common stock through brokers, dealers or agents who may receive compensation in the form of discounts, concessions or commissions from the selling stockholder and/or the purchasers of the shares of common stock for whom they may act as agent. In effecting sales, broker-dealers that are engaged by the selling stockholder may arrange for other broker-dealers to participate. Kingsbridge is an underwriter within the meaning of the Securities Act. Any brokers, dealers or agents who participate in the distribution of the shares of common stock may also be deemed to be underwriters, and any profits on the sale of the shares of common stock by them and any discounts, commissions or concessions received by any such brokers, dealers or agents may be deemed to be underwriting discounts and commissions under the Securities Act. Kingsbridge has advised us that it may effect resales of our common stock through any one or more registered broker-dealers. To the extent the selling stockholder may be deemed to be an underwriter, the selling stockholder will be subject to the prospectus delivery requirements of the Securities Act and may be subject to certain statutory liabilities of, including but not limited to, Sections 11, 12 and 17 of the Securities Act and Rule 10b-5 under the Exchange Act.

The selling stockholder will act independently of us in making decisions with respect to the timing, manner and size of each sale. Sales may be made over the Nasdaq Global Market, on the over-the-counter market, otherwise, or in a combination of such methods of sale, at then prevailing market prices, at prices related to prevailing market prices or at negotiated prices. The shares of common stock may be sold according to one or more of the following methods:

- a block trade in which the broker or dealer so engaged will attempt to sell the shares of common stock as agent but may position and resell a portion of the block as principal to facilitate the transaction;
- purchases by a broker or dealer as principal and resale by such broker or dealer for its account pursuant to this prospectus;
- an over-the-counter distribution in accordance with the rules of the Nasdaq;
- ordinary brokerage transactions and transactions in which the broker solicits purchasers;
- privately negotiated transactions;
- a combination of such methods of sale; and
- any other method permitted pursuant to applicable law.

Any shares covered by this prospectus which qualify for sale pursuant to Rule 144 of the Securities Act may be sold under Rule 144 rather than pursuant to this prospectus. In addition, the selling stockholder may transfer the shares by other means not described in this prospectus.

Any broker-dealer participating in such transactions as agent may receive commissions from Kingsbridge (and, if they act as agent for the purchaser of such shares, from the purchaser). Broker-dealers may agree with Kingsbridge to sell a specified number of shares at a stipulated price per share, and, to the extent a broker-dealer is unable to do so acting as agent for Kingsbridge, to purchase as principal any unsold shares at the price required to fulfill the broker-dealer commitment to Kingsbridge. Broker-dealers who acquire shares as principal may thereafter resell such shares from time to time in transactions (which may involve crosses and block transactions and which may involve sales to and through other broker-dealers, including transactions of the nature described above) on the Nasdaq Global Market, on the over-the-counter market, in privately-negotiated transactions or otherwise, at market prices prevailing at the time of sale or at negotiated prices, and in connection with such resales may pay to or receive from the purchasers of such shares commissions computed as described above. To the extent required under the Securities Act, an amendment to this prospectus, or a supplemental prospectus will be filed, disclosing:

- the name of any such broker-dealers;

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- the number of shares involved;
- the price at which such shares are to be sold;
- the commission paid or discounts or concessions allowed to such broker-dealers, where applicable;
- that such broker-dealers did not conduct any investigation to verify the information set out or incorporated by reference in this prospectus, as supplemented; and
- other facts material to the transaction.

Underwriters and purchasers that are deemed underwriters under the Securities Act may engage in transactions that stabilize, maintain or otherwise affect the price of the securities, including the entry of stabilizing bids or syndicate covering transactions or the imposition of penalty bids. Kingsbridge and any other persons participating in the sale or distribution of the shares will be subject to the applicable provisions of the Exchange Act and the rules and regulations thereunder including, without limitation, Regulation M. These provisions may restrict certain activities of, and limit the timing of, purchases by the selling stockholder or other persons or entities. Furthermore, under Regulation M, persons engaged in a distribution of securities are prohibited from simultaneously engaging in market making and certain other activities with respect to such securities for a specified period of time prior to the commencement of such distributions, subject to special exceptions or exemptions. Regulation M may restrict the ability of any person engaged in the distribution of the securities to engage in market-making and certain other activities with respect to those securities. In addition, the anti-manipulation rules under the Exchange Act may apply to sales of the securities in the market. All of these limitations may affect the marketability of the shares and the ability of any person to engage in market-making activities with respect to the securities.

We have agreed to pay the expenses of registering the shares of common stock under the Securities Act, including registration and filing fees, printing expenses, administrative expenses and certain legal and accounting fees, as well as certain fees of counsel for the selling stockholder incurred in the preparation of the CEFF agreements and the registration statement of which this prospectus forms a part. The selling stockholder will bear all discounts, commissions or other amounts payable to underwriters, dealers or agents, as well as transfer taxes and certain other expenses associated with the sale of securities.

Under the terms of the Kingsbridge common stock purchase agreement and the registration rights agreement, we have agreed to indemnify the selling stockholder and specified other persons against certain liabilities in connection with the offering of the shares of common stock offered hereby, including liabilities arising under the Securities Act or, if indemnity is unavailable, to contribute toward amounts required to be paid in respect of such liabilities.

At any time a particular offer of the shares of common stock is made, a revised prospectus or prospectus supplement, if required, will be distributed. Any prospectus supplement or post-effective amendment will be filed with the SEC, to reflect the disclosure of required additional information with respect to the distribution of the shares of common stock. We may suspend the sale of shares by the selling stockholder pursuant to this prospectus for specified periods of time for certain reasons, including if the prospectus is required to be supplemented or amended to include additional material information.

## LEGAL MATTERS

The validity of the securities being offered hereby will be passed upon by Cooley Godward Kronish LLP, San Diego, California. As of the date of this prospectus, investment funds affiliated with Cooley Godward Kronish LLP owned 8,230 shares of common stock and warrants to purchase 5,940 shares of common stock having a weighted average exercise price of \$7.44 per share.

## EXPERTS

Ernst & Young LLP, independent registered public accounting firm, has audited our financial statements included in our Annual Report on Form 10-K for the year ended December 31, 2005, as set forth in their report, which is incorporated by reference in this prospectus and elsewhere in the registration statement. Our financial statements are incorporated by reference in reliance on Ernst & Young LLP's report, given on their authority as experts in accounting and auditing.

## WHERE YOU CAN FIND MORE INFORMATION

We file annual, quarterly and special reports, proxy statements and other information with the SEC. Our SEC filings are available to the public over the Internet at the SEC's web site at <http://www.sec.gov>. You may also read and copy any document we file at the SEC's public reference room at 100 F Street, NE, Room 1580, Washington, D.C. 20549. You may obtain information on the operation of the SEC's public reference room in Washington, D.C. by calling the SEC at 1-800-SEC-0330.

The SEC allows us to incorporate by reference into this prospectus the information in documents we file with it, which means that we can disclose important information to you by referring you to those documents. Any statement contained in any document incorporated or deemed to be incorporated by reference herein shall be deemed to be modified or superseded, for purposes of this prospectus, to the extent that a statement contained in or omitted from this prospectus, or in any other subsequently filed document which also is or is deemed to be incorporated by reference herein, modifies or supersedes such statement. Any statement so modified or superseded shall not be deemed, except as so modified or superseded, to constitute a part of this prospectus. We incorporate by reference the documents listed below and any future filings we make with the SEC under Sections 13(a), 13(c), 14 or 15(d) of the Exchange Act until the offering is completed:

- Our Annual Report on Form 10-K for the year ended December 31, 2005 which was filed on March 23, 2006, including all material incorporated by reference therein;
- Our Quarterly Reports on Form 10-Q for the quarters ended March 31, 2006, June 30, 2006 and September 30, 2006 which were filed on May 11, 2006, August 11, 2006 and November 6, 2006, respectively;
- Our Current Reports on Form 8-K filed on March 27, 2006, July 25, 2006, September 14, 2006, October 30, 2006 and November 11, 2006 (except for the information furnished under Item 2.02 therein); and
- The description of our common stock contained in our Registration Statement on Form 8-A filed on May 28, 2004.

We will provide without charge to each person, including any beneficial owner, to whom this prospectus is delivered, upon written or oral request of such person, a copy of any and all of the documents that have been incorporated by reference in this prospectus (not including exhibits to such documents, unless such exhibits are specifically incorporated by reference in this prospectus or into such documents). Such request may be directed to Metabasis Therapeutics, Inc., 11119 North Torrey Pines Road, La Jolla, California 92037, (858) 587-2770.

All documents that we file with the SEC pursuant to Section 13(a), 13(c), 14 or 15(d) of the Exchange Act after the date of this prospectus and before the termination of the offering of the securities offered in this prospectus shall be deemed incorporated by reference into this prospectus and to be a part of this prospectus from the respective date of filing such documents.





We have filed with the SEC a registration statement on Form S-3 under the Securities Act covering the securities described in this prospectus. This prospectus does not contain or incorporate by reference all of the information included in the registration statement, some of which is contained in exhibits included with or incorporated by reference into the registration statement. The registration statement, including the exhibits contained or incorporated by reference therein, can be read at the SEC's web site or at the SEC's office referred to above. Any statement made or incorporated by reference in this prospectus concerning the contents of any contract, agreement or other document is only a summary of the actual contract, agreement or other document. If we have filed or incorporated by reference any contract, agreement or other document as an exhibit to the registration statement, you should read the exhibit for a more complete understanding of the document or matter involved. Each statement regarding a contract, agreement or other document is qualified in its entirety by reference to the actual document.

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**PART II****INFORMATION NOT REQUIRED IN PROSPECTUS****Item 14. Other Expenses of Issuance and Distribution**

The following table sets forth all expenses payable by the registrant in connection with the sale of the common stock being registered. The stockholders will not bear any portion of these expenses. All the amounts shown are estimates except for the registration fee.

SEC registration fee	\$	5,034
Legal fees and expenses	\$	30,000
Accounting fees and expenses	\$	10,000
Printing and miscellaneous expenses	\$	4,966
Total	\$	50,000

**Item 15. Indemnification of Directors and Officers**

We are incorporated under the laws of the State of Delaware. Section 145 of the Delaware General Corporation Law provides that a Delaware corporation may indemnify any persons who are, or are threatened to be made, parties to any threatened, pending or completed action, suit or proceeding, whether civil, criminal, administrative or investigative (other than an action by or in the right of such corporation), by reason of the fact that such person was an officer, director, employee or agent of such corporation, or is or was serving at the request of such person as an officer, director, employee or agent of another corporation or enterprise. The indemnity may include expenses (including attorneys' fees), judgments, fines and amounts paid in settlement actually and reasonably incurred by such person in connection with such action, suit or proceeding, provided that such person acted in good faith and in a manner he or she reasonably believed to be in or not opposed to the corporation's best interests and, with respect to any criminal action or proceeding, had no reasonable cause to believe that his or her conduct was illegal. A Delaware corporation may indemnify any persons who are, or are threatened to be made, a party to any threatened, pending or completed action or suit by or in the right of the corporation by reason of the fact that such person was a director, officer, employee or agent of such corporation, or is or was serving at the request of such corporation as a director, officer, employee or agent of another corporation or enterprise. The indemnity may include expenses (including attorneys' fees) actually and reasonably incurred by such person in connection with the defense or settlement of such action or suit provided such person acted in good faith and in a manner he or she reasonably believed to be in or not opposed to the corporation's best interests except that no indemnification is permitted without judicial approval if the officer or director is adjudged to be liable to the corporation. Where an officer or director is successful on the merits or otherwise in the defense of any action referred to above, the corporation must indemnify him or her against the expenses which such officer or director has actually and reasonably incurred. Our amended and restated certificate of incorporation and amended and restated bylaws provide for the indemnification of our directors and officers to the fullest extent permitted under the Delaware General Corporation Law.

Section 102(b)(7) of the Delaware General Corporation Law permits a corporation to provide in its certificate of incorporation that a director of the corporation shall not be personally liable to the corporation or its stockholders for monetary damages for breach of fiduciary duties as a director, except for liability:

- for any transaction from which the director derives an improper personal benefit;
- for acts or omissions not in good faith or that involve intentional misconduct or a knowing violation of law;
- for improper payment of dividends or redemptions of shares; or

- for any breach of a director's duty of loyalty to the corporation or its stockholders.

Our amended and restated certificate of incorporation and amended and restated bylaws include such a provision. Expenses incurred by any officer or director in defending any such action, suit or proceeding in advance of its final disposition shall be paid by us upon delivery to us of an undertaking, by or on behalf of such director or officer, to repay all amounts so advanced if it shall ultimately be determined that such director or officer is not entitled to be indemnified by us.

Section 174 of the Delaware General Corporation Law provides, among other things, that a director, who willfully or negligently approves of an unlawful payment of dividends or an unlawful stock purchase or redemption, may be held liable for such actions. A director who was either absent when the unlawful actions were approved, or dissented at the time, may avoid liability by causing his or her dissent to such actions to be entered in the books containing minutes of the meetings of the board of directors at the time such action occurred or immediately after such absent director receives notice of the unlawful acts.

As permitted by the Delaware General Corporation Law, we have entered into indemnity agreements with each of our directors and executive officers, that require us to indemnify such persons against any and all expenses (including attorneys' fees), witness fees, damages, judgments, fines, settlements and other amounts incurred (including expenses of a derivative action) in connection with any action, suit or proceeding, whether actual or threatened, to which any such person may be made a party by reason of the fact that such person is or was a director, an officer or an employee of Metabasis or any of its affiliated enterprises, provided that such person acted in good faith and in a manner such person reasonably believed to be in or not opposed to our best interests and, with respect to any criminal proceeding, had no reasonable cause to believe his or her conduct was unlawful. The indemnification agreements also set forth certain procedures that will apply in the event of a claim for indemnification thereunder.

At present, there is no pending litigation or proceeding involving any of our directors or executive officers as to which indemnification is required or permitted, and we are not aware of any threatened litigation or proceeding that may result in a claim for indemnification.

We have an insurance policy covering our officers and directors with respect to certain liabilities, including liabilities arising under the Securities Act of 1933, as amended, or otherwise.

Insofar as the indemnification for liabilities arising under the Securities Act may be permitted to directors, officers or persons controlling the registrant pursuant to the foregoing provisions, the registrant has been informed that in the opinion of the SEC such indemnification is against public policy as expressed in the Securities Act and is, therefore, unenforceable.

#### Item 16. Exhibits

Exhibit Number	Description of Document
2.1(1)	Asset and Liability Transfer Agreement dated December 17, 1997 between Metabasis Therapeutics, Inc. and Gensia Sicor Inc.
2.2(1)	Master Agreement dated June 30, 1999 among Metabasis Therapeutics, Inc., Sicor Inc., Paul K. Laikind, Mark D. Erion and John W. Beck.
4.1(1)	Form of Common Stock Certificate.
4.2(1)	Stock Purchase Warrant dated February 6, 2001 issued to GATX Ventures, Inc.
4.3(1)	Warrant to Purchase 26,000 Shares of Series C Preferred Stock dated February 6, 2001 issued to GATX Ventures, Inc., as amended July 26, 2001.
4.4(1)	Warrant to Purchase 19,000 Shares of Series C Preferred Stock dated July 26, 2001, issued to GATX Ventures, Inc.



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Exhibit Number	Description of Document
4.5(1)	Warrant to Purchase 30,666 Shares of Series D Preferred Stock dated April 8, 2002, issued to GATX Ventures, Inc.
4.6(1)	Form of Stock Purchase Warrant issued to participants in Metabasis Therapeutics, Inc. s Series C Preferred Stock financing dated July 18, 2000.
4.7(1)	Form of Stock Purchase Warrant issued to participants in Metabasis Therapeutics, Inc. s Series D Preferred Stock financing dated October 18, 2001.
4.8(1)	Form of letter agreement entered into between Metabasis Therapeutics, Inc. and its warrantholders.
4.9(1)	Letter agreement dated October 18, 2001 entered into between Metabasis Therapeutics, Inc. and Sprout Capital IX, L.P. and its affiliates.
4.11(1)	Amended and Restated Investors Rights Agreement dated October 28, 2003, as amended, between Metabasis Therapeutics, Inc. and certain of its stockholders.
4.12(2)	Securities Purchase Agreement dated September 30, 2005, by and among Metabasis Therapeutics, Inc. and the individuals and entities identified on Exhibit A thereto.
4.13(2)	Form of Warrant issued pursuant to the Securities Purchase Agreement.
4.14(3)	Warrant, dated November 2, 2006, issued by Metabasis Therapeutics, Inc. to Kingsbridge Capital Limited.
4.15(3)	Registration Rights Agreement, dated November 2, 2006, by and between Metabasis Therapeutics, Inc. and Kingsbridge Capital Limited.
10.1(3)	Common Stock Purchase Agreement, dated as of November 2, 2006, by and between Metabasis Therapeutics, Inc. and Kingsbridge Capital Limited.
5.1	Opinion of Cooley Godward Kronish LLP.
23.1	Consent of Independent Registered Public Accounting Firm.
23.2	Consent of Cooley Godward Kronish LLP (included in Exhibit 5.1).
24.1	Power of Attorney (included on signature page).

(1) Incorporated by reference to the exhibit of the same number to the Registration Statement on Form S-1 (No. 333-12437), originally filed on February 3, 2004.

(2) Incorporated by reference to the exhibit of the same number to the Company s Current Report on Form 8-K filed on October 5, 2005.

(3) Incorporated by reference to Exhibits 4.1, 4.2 and 10.1 to the Company s Current Report on Form 8-K filed on November 2, 2006.

**Item 17. Undertakings**

The undersigned registrant hereby undertakes:

(1) To file, during any period in which offers or sales are being made, a post-effective amendment to this registration statement:

(i) To include any prospectus required by Section 10(a)(3) of the Securities Act of 1933;

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(ii) To reflect in the prospectus any facts or events arising after the effective date of this registration statement (or the most recent post-effective amendment thereof) which, individually or in the aggregate, represent a fundamental change in the information set forth in the registration statement. Notwithstanding the foregoing, any increase or decrease in the volume of securities offered (if the total dollar value of securities offered would not exceed that which was registered) and any deviation from the low or high end of the estimated maximum aggregate offering range may be reflected in the form of prospectus filed with the SEC pursuant to Rule 424(b) if, in the aggregate, the changes in volume and price represent no more than 20 percent change in the maximum aggregate offering price set forth in the Calculation of Registration Fee table in the effective registration statement; and

(iii) To include any material information with respect to the plan of distribution not previously disclosed in the registration statement or any material change to such information in the registration statement;

*provided, however,* that paragraphs (1)(i), (1)(ii) and (1)(iii) of this section do not apply if the registration statement is on Form S-3 or Form F-3 and the information required to be included in a post-effective amendment by those paragraphs is contained in reports filed with or furnished to the SEC by the registrant pursuant to section 13 or section 15(d) of the Securities Exchange Act of 1934 that are incorporated by reference in the registration statement, or is contained in a form of prospectus filed pursuant to Rule 424(b) that is part of the registration statement.

(2) That, for the purpose of determining any liability under the Securities Act of 1933, each such post-effective amendment shall be deemed to be a new registration statement relating to the securities offered therein, and the offering of the securities at that time shall be deemed to be the initial *bona fide* offering thereof.

(3) To remove from registration by means of a post-effective amendment any of the securities being registered that remain unsold at the termination of the offering.

(4) That, for the purpose of determining liability under the Securities Act of 1933 to any purchaser:

If the registrant is subject to Rule 430C, each prospectus filed pursuant to Rule 424(b) as part of a registration statement relating to an offering, other than registration statements relying on Rule 430B or other than prospectuses filed in reliance on Rule 430A, shall be deemed to be part of and included in the registration statement as of the date it is first used after effectiveness. Provided, however, that no statement made in a registration statement or prospectus that is part of the registration statement or made in a document incorporated or deemed incorporated by reference into the registration statement or prospectus that is part of the registration statement will, as to a purchaser with a time of contract of sale prior to such first use, supersede or modify any statement that was made in the registration statement or prospectus that was part of the registration statement or made in any such document immediately prior to such date of first use.

Insofar as indemnification for liabilities arising under the Securities Act of 1933 may be permitted to directors, officers, and controlling persons of the registrant pursuant to the foregoing provisions, or otherwise, the registrant has been advised that in the opinion of the SEC such indemnification is against public policy as expressed in the Securities Act of 1933 and is, therefore, unenforceable. In the event that a claim for indemnification against such liabilities (other than the payment by the registrant of expenses incurred or paid by a director, officer, or controlling person of the registrant in the successful defense of any action, suit or proceeding) is asserted by such director, officer, or controlling person in connection with the securities being registered, the registrant will, unless in the opinion of its counsel the matter has been settled by controlling precedent, submit to a court of appropriate jurisdiction the question whether such indemnification by it is against public policy as expressed in the Securities Act and will be governed by the final adjudication of such issue.



**SIGNATURES**

Pursuant to the requirements of the Securities Act of 1933, as amended, the registrant certifies that it has reasonable grounds to believe that it meets all of the requirements for filing on Form S-3 and has duly caused this registration statement to be signed on its behalf by the undersigned, thereunto duly authorized, in the City of La Jolla, State of California, on the 15th day of November, 2006.

**METABASIS THERAPEUTICS, INC.**

By: */s/ Paul K. Laikind, Ph.D.*  
Paul K. Laikind, Ph.D.  
*President and Chief Executive Officer*

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**KNOW ALL PERSONS BY THESE PRESENTS**, that each person whose signature appears below constitutes and appoints Paul K. Laikind, Ph.D. and John W. Beck, C.P.A., and each of them, as his or her true and lawful attorneys-in-fact and agents, with full power of substitution and resubstitution, for him or her and in his or her name, place, and stead, in any and all capacities, to sign any and all amendments (including post-effective amendments, exhibits thereto and other documents in connection therewith) to this registration statement, and to file the same, with all exhibits thereto, and other documents in connection therewith (including any registration statement relating to this registration statement and filed pursuant to Rule 462(b) of the Securities Act of 1933, as amended), with the Securities and Exchange Commission, granting unto said attorneys-in-fact and agents, and each of them, full power and authority to do and perform each and every act and thing requisite and necessary to be done in connection therewith, as fully to all intents and purposes as he or she might or could do in person, hereby ratifying and confirming all that said attorneys-in-fact and agents, or either of them, or their or his substitute or substitutes, may lawfully do or cause to be done by virtue hereof.

Pursuant to the requirements of the Securities Act of 1933, as amended, this registration statement has been signed below by the following persons in the capacities and on the dates indicated.

<b>Date</b>	<b>Signature</b>	<b>Title</b>
November 15, 2006	/s/ Paul K. Laikind, Ph.D. Paul K. Laikind, Ph.D.	President, Chief Executive Officer and Secretary ( <i>Principal Executive Officer</i> )
November 15, 2006	/s/ John W. Beck, C.P.A. John W. Beck, C.P.A.	Senior Vice President of Finance, Chief Financial Officer and Treasurer ( <i>Principal Financial and Accounting Officer</i> )
November 15, 2006	/s/ David F. Hale David F. Hale	Chairman of the Board
November 15, 2006	/s/ Daniel D. Burgess, M.B.A. Daniel D. Burgess, M.B.A.	Director
November 15, 2006	/s/ Mark D. Erion, Ph.D. Mark D. Erion, Ph.D.	Executive Vice President of Research and Development, Chief Scientific Officer and Director
November 15, 2006	/s/ Luke B. Evnin, Ph.D. Luke B. Evnin, Ph.D.	Director
November 15, 2006	/s/ Heinz W. Gschwend, Ph.D. Heinz W. Gschwend, Ph.D.	Director
November 15, 2006	/s/ Arnold L. Oronsky, Ph.D. Arnold L. Oronsky, Ph.D.	Director
November 15, 2006	/s/ William R. Rohn William R. Rohn	Director

## INDEX TO EXHIBITS

Exhibit Number	Description of Document
2.1(1)	Asset and Liability Transfer Agreement dated December 17, 1997 between Metabasis Therapeutics, Inc. and Gensia Sicor Inc.
2.2(1)	Master Agreement dated June 30, 1999 among Metabasis Therapeutics, Inc., Sicor Inc., Paul K. Laikind, Mark D. Erion and John W. Beck.
4.1(1)	Form of Common Stock Certificate.
4.2(1)	Stock Purchase Warrant dated February 6, 2001 issued to GATX Ventures, Inc.
4.3(1)	Warrant to Purchase 26,000 Shares of Series C Preferred Stock dated February 6, 2001 issued to GATX Ventures, Inc., as amended July 26, 2001.
4.4(1)	Warrant to Purchase 19,000 Shares of Series C Preferred Stock dated July 26, 2001, issued to GATX Ventures, Inc.
4.5(1)	Warrant to Purchase 30,666 Shares of Series D Preferred Stock dated April 8, 2002, issued to GATX Ventures, Inc.
4.6(1)	Form of Stock Purchase Warrant issued to participants in Metabasis Therapeutics, Inc.'s Series C Preferred Stock financing dated July 18, 2000.
4.7(1)	Form of Stock Purchase Warrant issued to participants in Metabasis Therapeutics, Inc.'s Series D Preferred Stock financing dated October 18, 2001.
4.8(1)	Form of letter agreement entered into between Metabasis Therapeutics, Inc. and its warrant holders.
4.9(1)	Letter agreement dated October 18, 2001 entered into between Metabasis Therapeutics, Inc. and Sprout Capital IX, L.P. and its affiliates.
4.11(1)	Amended and Restated Investors' Rights Agreement dated October 28, 2003, as amended, between Metabasis Therapeutics, Inc. and certain of its stockholders.
4.12(2)	Securities Purchase Agreement dated September 30, 2005, by and among Metabasis Therapeutics, Inc. and the individuals and entities identified on Exhibit A thereto.
4.13(2)	Form of Warrant issued pursuant to the Securities Purchase Agreement.
4.14(3)	Warrant, dated November 2, 2006, issued by Metabasis Therapeutics, Inc. to Kingsbridge Capital Limited.
4.15(3)	Registration Rights Agreement, dated November 2, 2006, by and between Metabasis Therapeutics, Inc. and Kingsbridge Capital Limited.
10.1(3)	Common Stock Purchase Agreement, dated as of November 2, 2006, by and between Metabasis Therapeutics, Inc. and Kingsbridge Capital Limited.
5.1	Opinion of Cooley Godward Kronish LLP.
23.1	Consent of Independent Registered Public Accounting Firm.
23.2	Consent of Cooley Godward Kronish LLP (included in Exhibit 5.1).

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24.1		Power of Attorney (included on signature page).

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(1) Incorporated by reference to the exhibit of the same number to the Registration Statement on Form S-1 (No. 333-12437), originally filed on February 3, 2004.

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- (2) Incorporated by reference to the exhibit of the same number to the Company's Current Report on Form 8-K filed on October 5, 2005.
- (3) Incorporated by reference to Exhibits 4.1, 4.2 and 10.1 to the Company's Current Report on Form 8-K filed on November 2, 2006.

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