

METABASIS THERAPEUTICS INC

Form 424B3

October 27, 2005

**Filed Pursuant to Rule 424(b)(3)**

**Registration File No. 333-129028**

**PROSPECTUS**

**9,450,000 Shares**

**Common Stock**

This prospectus relates to the offer and sale, from time to time, of up to 9,450,000 shares of Metabasis Therapeutics, Inc. common stock held by the selling stockholders listed on page 26 of this prospectus, including common stock issuable upon exercise of warrants. The selling stockholders purchased common stock and warrants to purchase common stock from us in a private placement that closed in September 2005. We will not receive any proceeds from the sale of the shares by the selling stockholders.

For a description of the plan of distribution of the shares, see page 32 of this prospectus.

Our common stock is listed on The Nasdaq National Market under the symbol MBRX. On October 27, 2005, the last reported sale price for our common stock was \$6.05 per share.

**Our business and an investment in our common stock involve significant risks. These risks are described under the caption Risk Factors beginning on page 2 of this prospectus.**

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or determined if this prospectus is truthful or complete. Any representation to the contrary is a criminal offense.

The date of this prospectus is October 27, 2005.



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**You should rely only on the information contained or incorporated by reference in this prospectus and any applicable prospectus supplement. We have not, and the selling stockholders have not, authorized anyone to provide you with additional information or information different from that contained or incorporated by reference in this prospectus and any applicable prospectus supplement. The selling stockholders are offering to sell, and seeking offers to buy, shares of our common stock only in jurisdictions where offers and sales are permitted.**

**The information contained in this prospectus is accurate only as of the date of this prospectus and information appearing in any applicable prospectus supplement is accurate only as of the date of the applicable prospectus supplement. Additionally, information from other documents incorporated by reference in this prospectus or any applicable prospectus supplement is accurate only as of the date of the document incorporated by reference, regardless of the time of delivery of the prospectus or prospectus supplement 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 appearing under 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 currently have three product candidates in clinical development, CS-917, pradefovir and MB07133, which are being developed for the treatment of type 2 diabetes, hepatitis B and primary liver cancer, respectively. In addition to these product candidates, we have two clinical development candidates, MB07803 and MB07811, which have been recommended for clinical development. MB07803 is a clinical development candidate for the treatment of type 2 diabetes that works by the same mechanism as CS-917. MB07811 is a clinical development candidate for the treatment of high cholesterol and possibly obesity that acts through a liver mechanism. We plan to file Investigational New Drug Applications for, and expect to commence clinical trials of, both MB07803 and MB07811 in 2006.

All our product candidates and clinical development candidates have been discovered at Metabasis and our discovery efforts are continuing. In addition to our product candidates and clinical development candidates, we have research programs focused on metabolic diseases linked to pathways in the liver such as type 2 diabetes, hyperlipidemia and obesity, as well as liver diseases such as hepatitis C and liver fibrosis. We are developing CS-917 and pradefovir in collaboration with Sankyo Co., Ltd. and Valeant Pharmaceuticals International, respectively. We are independently developing and currently retain all rights to MB07133, MB07803 and MB07811.

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.

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Our principal offices are located at 11119 North Torrey Pines Road, La Jolla, CA 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. 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.

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## RISK FACTORS

*You should consider carefully the following information about the risks described below, together with the other information contained or incorporated by reference in this prospectus, before you decide to invest in our common stock. We believe the risks described below are the risks that are material to us as of the date of this prospectus. If any of the following risks actually occur, our business, financial condition, results of operations and future growth prospects would likely be materially and adversely affected. In these circumstances, the market price of our common stock could decline, and you may lose all or part of the money you paid to buy our common stock.*

### Risks Related to our Business

*We are dependent on the success of one or more of our current product candidates and clinical development 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 three current product candidates, CS-917, pradefovir and MB07133, and our two current clinical development candidates, MB07803 and MB07811. To date, clinical trials with CS-917 have demonstrated it was capable of significantly lowering blood glucose levels in type 2 diabetics. Likewise, clinical trials conducted to date in patients treated with pradefovir have provided strong evidence of efficacy as measured by clinically and statistically significant reductions in serum HBV DNA. Recent interim results from a Phase IIb study indicated that pradefovir produced greater viral load reductions than the marketed drug Hepsera®. However, our product candidates will require additional development, clinical trials and regulatory clearances before they can be commercialized. Positive results from pre-clinical studies and early clinical trials do not necessarily mean later clinical trials will succeed. Before we can market any of our product candidates or clinical development candidates, we will need to demonstrate that they are safe and effective in humans, and we will also need to obtain necessary marketing approval from the U.S. Food and Drug Administration, or FDA, or similar foreign regulatory agencies. Our product development efforts may not lead to commercial drugs, either because our product candidates or clinical development 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 process. 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 or clinical development 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 or clinical development candidates, we may be unable to commercialize them successfully for a variety of reasons. These include, for example, the availability of alternative treatments, 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 or clinical development 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 or clinical development 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 will be unable to commercialize these products.*

To receive regulatory approval for the commercialization of CS-917, pradefovir, MB07133 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 FDA in the U.S. and other regulatory agencies elsewhere in the world. In order to support marketing approval, these agencies typically require

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successful results in one or more Phase III 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:

our clinical trials may produce negative or inconclusive results,

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patient recruitment and enrollment in our clinical trials may be slower than we anticipate,

costs of our 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 pre-clinical 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 we have conducted tests in less than the number of patients that will likely need to be studied to gain regulatory approval of these product candidates. 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 CS-917 and pradefovir have been, and will continue to be, primarily established by Sankyo and Valeant, respectively. We are solely responsible for establishing the targeted endpoints for clinical trials of MB07133. 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, pre-clinical 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 can lead to lactic acidosis, a serious and potentially fatal condition. Certain pre-clinical animal studies have shown that CS-917 raises



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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 II 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 study. However, one patient who received 200 milligrams of CS-917 twice a day was withdrawn from the study 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.

In March 2005, we were notified by Sankyo that two serious adverse events involving lactic acidosis had occurred in two patients in a clinical trial evaluating the interaction of CS-917 with the marketed diabetes drug metformin. The serious adverse events were resolved after medical intervention. The two patients were administered CS-917 in combination with metformin. Three clinical trials that were ongoing at the time were stopped while one clinical trial which did not combine CS-917 with metformin continued and was completed. It was subsequently

determined that the two patients that experienced the lactic acidosis had blood levels of metformin that were elevated compared to other patients in the study that 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 lactic acidosis. CS-917 blood levels also rose higher than expected. In July 2005, after completing a comprehensive review of the program and the events and data surrounding the two serious adverse events, we and Sankyo concluded that the lactic acidosis observed in the two patients was likely due to the significantly increased blood levels of metformin described above. Subsequently, Sankyo decided that full development of CS-917 could safely resume pending discussions of the proposed plans and protocols with the FDA. We expect Sankyo to commence a Phase IIb study of CS-917, which will allow measurement of the regulatory endpoint HbA1c, in the fourth quarter of 2005. In addition, we expect Sankyo to 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 combination of CS-917 and metformin is not likely unless additional data suggests lactic acidosis can be avoided through patient exclusion or through the administration of CS-917 at lower doses or through other means. In addition, based on the results of this comprehensive review we have resumed development of our second-generation product candidate for diabetes, MB07803, and we expect to commence clinical trials of this product candidate early in 2006.

It is also possible that CS-917 and MB7803 may cause other side effects. In certain pre-clinical 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 tested to date in patients (400 milligrams twice a day). This dose is above what is expected to be used in Phase III 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 pre-clinical 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 pradevir 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.

In addition, undesirable side effects seen in the clinical trials of our product candidates, such as those recently observed with CS-917 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,

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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,

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 dependent on our collaborations with Sankyo and Valeant for development of CS-917 and pradefovir, respectively, and events involving these collaborations, our collaborations with Merck, 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 Sankyo and Valeant for the development and commercialization of CS-917 and pradefovir, respectively. Sankyo and Valeant have agreed to finance the clinical trials for CS-917 and pradefovir, respectively, and, if they are approved, manufacture and market them. Accordingly, we are dependent on Sankyo and Valeant to gain FDA and other foreign regulatory agency approval of, and to commercialize, CS-917 and pradefovir. We have also entered into two collaborations with Merck & Co., Inc. 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. Although our collaborations with Merck have not yet yielded any product candidates, should they be successful, we will be dependent on Merck 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, we may

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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.

We have limited control over the amount and timing of resources that Sankyo, Valeant, Merck 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 would 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 Sankyo contains certain rights and restrictions regarding our access to and use of confidential data and information generated by Sankyo. We are developing MB07803, a second-generation gluconeogenesis inhibitor to which 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 of confidential information and data related to CS-917 from 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 Sankyo, (ii) influence decisions made at Sankyo regarding CS-917, and (iii) accurately track 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.

*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 is to discover product candidates for the treatment of this disease by applying our technology to certain Merck compounds. Accordingly, if Merck terminates this collaboration before a defined stage of development of a product candidate, which it may do without cause at any time after the end of the collaboration's research term 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 be 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 Sankyo, Valeant, Merck 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 agreement with Sankyo contains certain rights and restrictions regarding our access to and use of confidential data and information generated by Sankyo. MB07803 is our second-generation gluconeogenesis inhibitor to which 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 of confidential information and data related to CS-917 from 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 Sankyo, (ii) influence decisions made at Sankyo regarding CS-917, and (iii) accurately track Sankyo's diligence on the development program. It could also lead to disagreements between Sankyo and us.

*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



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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 be effective or safe for their designated use, which would prevent their advancement into clinical trials and 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 testing could result in increased costs to us and delay our ability to generate significant revenues.*

Delays in the commencement or completion of clinical testing 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:

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obtaining regulatory approval to commence a clinical trial,

reaching agreement on acceptable terms with prospective contract research organizations and trial sites,

manufacturing sufficient quantities of a product candidate,

obtaining institutional review board approval to conduct a clinical trial at a prospective site, and

recruiting and enrolling patients to participate in a clinical trial.

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 trial site by the FDA or other regulatory authorities resulting in the imposition of a clinical hold,

unforeseen safety issues such as the serious adverse events recently observed in a clinical trial of CS-917, 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. For example, recent events related to CS-917 have delayed our clinical timeline for CS-917 as well as our second-generation gluconeogenesis inhibitor, MB07803. 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.*

Sankyo and Valeant are responsible for conducting clinical trials of CS-917 and pradefovir, 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. 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 and other product candidates that we may develop for which a collaborator is not responsible for clinical development. If Sankyo, Valeant, Merck 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 NuMimetic technology to identify CS-917 and MB07803, and our HepDirect technology to discover pradefovir and MB07133. 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 collaboration with Merck in which we are applying our technology to certain Merck 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 pre-clinical 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,

impose civil or criminal penalties,

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 will face significant competition from various formulations of metformin and products containing metformin. 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. Bristol-Myers-Squibb also markets Glucovance®, a single pill that contains both metformin and the insulin secretion enhancer glyburide. Biovail Corp. and DepoMed Inc. recently launched Glumetza , a once-daily, extended-release formulation of metformin hydrochloride. In addition, a less expensive generic form of metformin recently became available. Accordingly, unless CS-917 and/or 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 Sankyo to market CS-917 and/or for us to market MB07803. Other competitors to CS-917 and MB07803 may include, but are not limited to, the insulin sensitizers Actos® (pioglitazone), co-marketed by Takeda Chemical Industries, Ltd. and Eli Lilly and Company, Avandia® (rosiglitazone), marketed by GlaxoSmithKline PLC, Byetta (exenatide) injection, marketed by Amylin Pharmaceuticals and Eli Lilly , and other products that may be developed from time to time. GlaxoSmithKline has combined metformin and Avandia in a single pill called Avandamet®.

Competitors to pradeфовir may include, but are not limited to: Intron® A (interferon alfa-2b), marketed by Schering-Plough Corporation, Epivir-HBV® and Zeffix® (lamivudine), marketed by GlaxoSmithKline, Hepsера (adefovir dipivoxil), marketed in the U.S. by Gilead Sciences, Inc., and Baraclude (entecavir), marketed by Bristol-Myers Squibb Company. Pradeфовir and Hepsера are prodrugs of the same active drug, and therefore will directly compete. In order to effectively compete with Hepsера, pradeфовir may have to be significantly more beneficial or less expensive than Hepsера.

There are no currently approved drugs for primary liver cancer. However, there are potential competitors and treatments which may include, but are not limited to: Bayer Pharmaceuticals Corp. and Onyx Pharmaceuticals Inc., which have begun a Phase III clinical trial of sorafenib in patients with advanced liver cancer; Amgen Inc., which may be developing a product candidate called T67 currently in Phase II/III trials for the treatment of primary liver cancer; and other products that may be developed from time to time. We will also compete with non-surgical therapies that use either radioactive microscopic beads (such as TheraSpheres®) or chemotherapy (known as Transcatheter Arterial Chemoembolization (TACE)) injected through a catheter directly into the liver.

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 very large share of the hyperlipidemia market. The major drugs currently marketed for the treatment of hyperlipidemia are statins (cholesterol-reducers), including Lipitor® (\$10.9 billion in sales in 2004; marketed by Pfizer Inc.) and Zocor® (\$5.2 billion in sales in 2004; marketed by Merck), which were also two of the best selling prescription medicines in 2004.

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, pre-clinical 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 testing and eventual commercialization. Sankyo and Valeant are responsible for all clinical and commercial manufacturing of CS-917 and pradefovir, respectively. We have relied on a number of suppliers to manufacture sufficient quantities of MB07133 for use in our current clinical trial. 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. Similarly, we rely on outside manufacturing for MB07803 and MB07811. 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. We cannot estimate these costs with certainty but do not expect them to be material. In addition, any resulting interruption or delay we experience in the supply of MB07133, MB07803 or MB07811 may impede the clinical development of these compounds.

In addition, we, our collaborators or other third-party manufacturers of our products must comply with current good manufacturing practice, 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 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. Sankyo and Valeant are responsible for worldwide marketing and commercialization for CS-917 and pradefovir, respectively, although we have an option to co-promote CS-917 in North America with 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). In order to co-promote any of these products, or to commercialize MB07133 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

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co-promotion option under the metabolic disease collaboration developing a sales force 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, such as the serious adverse events recently observed in a clinical trial of CS-917,

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 pradefovir and MB07133 may also

exhibit interactions with other marketed drugs that could limit their combination with those drugs. Serious adverse events recently observed in a 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 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 prevent us from achieving 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 payors 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.

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 was recently enacted. This legislation provides a new Medicare prescription drug benefit beginning 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 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 93 as of June 30, 2005. 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 any principal member of our management or scientific staff, particularly Paul K. Laikind, Ph.D., our Chairman of the Board, Chief Executive Officer and President, and Mark D. Erion, Ph.D., our Executive Vice President of Research and Development, 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 continue to expand our manufacturing, research and development activities. 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. We are not currently a party to any agreements or commitments and we have no understandings with respect to any such acquisitions. 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 at all.*

We have incurred net losses from our inception. As of June 30, 2005, we had an accumulated deficit of approximately \$63.3 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 at all.

*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 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, including costs related to our relocation to our new facility in the fourth quarter of 2005,

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 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 may 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, debt financings or corporate collaboration and licensing arrangements. To the extent that we raise additional capital by issuing equity securities, 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, and

our execution of collaborative, licensing or other arrangements, and the timing of payments we may make or receive under these arrangements.

For example, our announcement of serious adverse events recently observed in a clinical trial of CS-917 had a significant negative impact on our stock price. 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 hepatitis B 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 other countries. We may not be able to develop patentable products or processes in the U.S. and other countries, and may not be able to obtain patents from pending applications. Even if patent claims are allowed in the U.S. and 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 also 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 Hepsera that is a non-liver specific prodrug of adefovir. Adefovir is covered by U.S. and foreign



patents that are scheduled to expire in April 2006. On their face, these patents are assigned to Gilead. We currently anticipate that, if approved, pradefovir will not be commercialized until after April 2006, and therefore should not infringe upon these patents. However, in some cases, the terms of U.S. and foreign patents covering drug products approved for commercialization may be extended if the holder of the patents requests an extension within a specified period following the date of regulatory approval and the request for extension is approved by the appropriate agencies. We are not aware that the term of the U.S. patents covering adefovir was extended following regulatory approval of Hepsera in the U.S., and the period in which extensions may have been requested has ended. The extension of any patent covering adefovir may prevent the commercialization of pradefovir in the relevant country until the expiration of the extended patent term, unless we or Valeant obtained a license to this patent. We are not aware of any request for an extension of patents covering adefovir in Europe.

We are aware of third party patents and patent applications in European and other foreign countries with claims to prodrugs of adefovir. These patents are scheduled to expire in September 2011. 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 foreign countries, including those in Europe. Further, we are aware that a patent term extension of one of these prodrug patents has been requested in one or more European countries based on the regulatory approval of Hepsera. If the extension request is granted, the patents would expire in September 2016. If granted, this extension may have an adverse impact on the commercialization of pradefovir in any such country if it is determined that the patent claims are valid and cover pradefovir. Additional third party patents covering Hepsera or adefovir may exist, and may expire later than April 2006 in the U.S. and later than 2011 in foreign countries.

#### **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.

The radioactive isotopes and compounds we use can cause radiation contamination to our facility. State and federal laws require that before permanently leaving a facility in which radioactive materials have been used, the user of the radioactive materials must make certain that the facility passes a series of tests known as decommissioning. The decommissioning process is highly regulated and may be expensive. In connection with our move to a new facility in the fourth quarter of 2005, we have incurred, and will continue to incur, costs in the decommissioning of our old facility. We cannot predict the ultimate amount of these costs, and they may be substantial.

*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, two cases of lactic acidosis were recently 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 us to enact various risk management programs to avoid its inadvertent use with metformin. 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. However, we do not carry specific biological or hazardous waste insurance coverage and 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. Accordingly, in the event of contamination or injury, we could be held liable for damages or penalized with fines in an amount exceeding our 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 part because our shares have only recently been traded publicly. 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 Sankyo, Valeant, 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,

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.

For example, our announcement of serious adverse events recently observed in a clinical trial of CS-917 had a significant negative impact on our stock price.

***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 acquirors 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.

***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 73% of our common stock as of June 30, 2005. 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 3,797,176 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. Sales by these stockholders or warrant holders of a substantial number of shares could significantly reduce the market price of our common stock.

### FORWARD-LOOKING STATEMENTS

This prospectus and the documents incorporated by reference contain forward-looking statements that are based on our management's beliefs and assumptions and on information currently available to our management. Forward-looking statements include information concerning our possible or assumed future results of operations, business strategies, financing plans, competitive position, industry environment, potential growth opportunities, the effects of future regulation and the effects of competition. 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, plans, projects, should, will, would or similar expressions.

Forward-looking statements involve known and unknown risks, uncertainties and other factors which may cause our actual results, performance or achievements to be materially different from any future results, performances or achievements expressed or implied by the forward-looking statements. We discuss these risks in greater detail in Risk Factors. Given these uncertainties, you should not place undue reliance on these forward-looking statements. Also, forward-looking statements represent our management's beliefs and assumptions only as of the date of this prospectus. You should read this prospectus and the documents that we reference in this prospectus and have filed as exhibits to the registration statement, of which this prospectus is a part, completely and with the understanding that our actual future results may be materially different from what we expect.

Except as required by law, we assume no obligation to update these forward-looking statements publicly, or to update the reasons actual results could differ materially from those anticipated in these forward-looking statements, even if new information becomes available in the future. The forward-looking statements contained in this prospectus are excluded from the safe harbor protection provided by the Private Securities Litigation Reform Act of 1995 and Section 27A of the Securities Act of 1933, as amended, or the Securities Act.



### USE OF PROCEEDS

We will not receive any proceeds from the sale of shares of our common stock by the selling stockholders. The proceeds from the sale of the common stock offered pursuant to this prospectus are solely for the accounts of the selling stockholders.

The selling stockholders will pay any underwriting discounts and commissions and expenses incurred by the selling stockholders for brokerage, accounting, tax or legal services or any other expenses incurred by the selling stockholders in disposing of the shares. We will bear all other costs, fees and expenses incurred in effecting the registration of the shares covered by this prospectus, including, without limitation, all registration and filing fees and fees and expenses of our counsel and our accountants.

A portion of the shares covered by this prospectus are issuable upon exercise of warrants to purchase our common stock. Upon any exercise for cash of the warrants, the selling stockholders will pay us the exercise price of the warrants. The cash exercise price of the warrants is \$6.74 per share of our common stock. The warrants are also exercisable on a cashless basis. We will not receive any cash payment from the selling stockholders upon any exercise of the warrants on a cashless basis.

**SELLING STOCKHOLDERS**

We are registering for resale shares of our common stock which have been sold to the selling stockholders identified below or that may be issued upon exercise of the warrants which have been issued to the selling stockholders identified below. Pursuant to a securities purchase agreement dated as of September 30, 2005 among us and the selling stockholders, we issued and sold, for an aggregate purchase price of approximately \$41.3 million:

an aggregate of 7,000,000 shares of our common stock, and

warrants to purchase an aggregate of 2,450,000 shares of our common stock at an exercise price of \$6.74 per share, which warrants become exercisable 180 days following the date of issuance and expire five years from the date of issuance.

The table below presents information regarding the selling stockholders and the shares that they may offer and sell from time to time under this prospectus. The shares of common stock covered, as to their resale, under this prospectus include shares of common stock sold in the financing and issuable upon exercise of warrants sold in the financing.

This table is prepared based in part on information supplied to us by the selling stockholders identified below as of September 30, 2005. 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, and assumes the exercise of all the warrants for common stock issued under the September 30, 2005 securities purchase agreement. In addition, the table assumes that the selling stockholders sell all of such shares. However, because the selling stockholders may offer from time to time all or some of their shares under this prospectus, or in another permitted manner, we cannot assure you as to the actual number of shares that will be sold by the selling stockholders or that will be held by the selling stockholders after completion of the sales. Information concerning the selling stockholders may change from time to time and changed information will be presented in a supplement to this prospectus if and when necessary and required.

Beneficial ownership is determined in accordance with Rule 13d-3(d) promulgated by the Securities and Exchange Commission under the Securities Exchange Act of 1934, as amended, or the Exchange Act, except that it also includes warrants held by the selling stockholders that become exercisable greater than 60 days following September 30, 2005.

Selling Stockholders	Shares Beneficially Owned Prior to Offering (1)		Number of Shares Being Offered (2)	Shares Beneficially Owned After Offering (1)	
	Number	Percent		Number	Percent
14159, L.P. (3)	18,853	*	14,681	4,172	*
Baker Biotech Fund I, L.P. (4)	214,830	*	60,571	154,259	*
Baker Biotech Fund II (Z), L.P.(5)	44,048	*	24,719	19,329	*
Baker Biotech Fund II, L.P. (6)	229,769	*	88,488	141,281	*
Baker Biotech Fund III (Z), L.P. (7)	57,595	*	40,229	17,366	*
Baker Biotech Fund III, L.P. (8)	315,758	1.2%	196,575	119,183	*

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Baker Bros. Investments II, L.P. (9)	20,448	*	5,390	15,058	*
Biotechnology Value Fund II (10)(11)	109,269	*	109,269		
Biotechnology Value Fund, L.P. (11)(12)	172,530	*	172,530		
BVF Investments, LLC (11)(13)	264,546	1.0%	264,546		
Capital Ventures International (14)	229,500	*	229,500		
Deerfield International Limited (15)	494,416	1.9%	494,416	50,856	*
Deerfield Partners, L.P. (16)	456,384	1.8%	409,440	46,944	*
DLJ Capital Corporation (17)(18)	26,589	*	5,202	21,387	*
Domain Public Equity Partners, L.P. (19)	344,250	1.4%	344,250		
Federated Kaufmann Fund, A Portfolio of Federated Equity Funds (20)	3,454,650	13.2%	3,454,650		
InterWest Investors VII, L.P. (21)(22)	145,612	*	26,321	119,291	*
InterWest Partners VII, L.P. (22)(23)	3,040,686	11.8%	549,617	2,491,069	9.7%
Investment 10, LLC (11)(24)	28,755	*	28,755		
Judith S. Sandler (25)	22,950	*	22,950		
Maverick Fund II, Ltd. (26)	547,305	2.2%	339,803	207,502	*
MPM Asset Management Investors 2000 B LLC (27)(28)	83,878	*	14,640	69,238	*
MPM BioVentures GmbH & Co. Parallel-Beteiligungs KG (28)(29)	1,282,585	5.0%	223,856	1,058,729	4.2%
MPM BioVentures II, L.P. (28)(30)	401,991	1.6%	70,180	331,811	1.3%
MPM BioVentures II-QP, L.P. (28)(31)	3,643,164	14.1%	635,864	3,007,300	11.7%
Red Abbey Venture Partners (QP), L.P. (32)(33)	172,897	*	172,897		
Red Abbey Venture Partners, L.P. (33)(34)	48,102	*	48,102		
Red Abbey CEO s Fund, L.P. (33)(35)	9,376	*	9,376		
Special Situations Cayman Fund L.P. (36)(37)	151,035	*	46,035	105,000	*
Special Situations Fund III, L.P. (37)(38)	599,740	2.4%	184,140	415,600	1.6%
Special Situations Private Equity Fund L.P.(37) (39)	230,175	*	230,175		
Sprout Capital IX, L.P. (18)(40)	2,203,966	8.6%	434,024	1,769,942	6.9%
Sprout Entrepreneurs Fund, L.P. (18)(41)	8,684	*	1,710	6,974	*
Sprout IX Plan Investors, L.P. (18)(42)	116,136	*	19,815	96,321	*
Tang Capital Partners, L.P. (43)	237,650	*	229,500	8,150	*

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\* Less than 1%

(1) Shares beneficially owned include (a) shares of common stock and (b) shares of common stock issuable upon exercise of warrants. Percentages are based on 25,235,013 shares of our common stock that were outstanding on September 30, 2005. In calculating the percentage for each selling security holder, the shares represented by item (b) above are treated as shares outstanding for that selling security holder but are not treated as outstanding for any other person.

(2) Number of shares beneficially owned include 2,450,000 shares of common stock issuable upon exercise of warrants received pursuant to the September 30, 2005 securities purchase agreement that are not currently exercisable within 60 days of September 30, 2005 but that will become exercisable 180 days after September 30, 2005.

(3) Includes 3,806 shares of common stock issuable upon exercise of warrants received in connection with the September 30, 2005 securities purchase agreement. Julian Baker and Felix Baker are managing members of 14159 Capital, L.P. and 14159 Capital (GP), LLC, the general partners of 14159, L.P., and disclaim beneficial ownership of the shares except to the extent of their pecuniary interest therein.

(4) Includes 15,703 shares of common stock issuable upon exercise of warrants received in connection with the September 30, 2005 securities purchase agreement. Julian Baker and Felix Baker are managing members of Baker Biotech Capital, L.P. and Baker Biotech Capital (GP), LLC, the general partners of Baker Biotech Fund I, L.P., and disclaim beneficial ownership of the shares except to the extent of their pecuniary interest therein.

(5) Includes 6,409 shares of common stock issuable upon exercise of warrants received in connection with the September 30, 2005 securities purchase agreement. Julian Baker and Felix Baker are managing members of Baker Biotech Capital II (Z), L.P. and Baker Biotech Capital II (Z) (GP), LLC, the general partners of Baker Biotech Fund II (Z), L.P., and disclaim beneficial ownership of the shares except to the extent of their pecuniary interest therein.

(6) Includes 22,942 shares of common stock issuable upon exercise of warrants received in connection with the September 30, 2005 securities purchase agreement. Julian Baker and Felix Baker are managing members of Baker Biotech Capital II, L.P. and Baker Biotech Capital II (GP), LLC, the general partners of Baker

Biotech Fund II, L.P., and disclaim beneficial ownership of the shares except to the extent of their pecuniary interest therein.

(7) Includes 10,430 shares of common stock issuable upon exercise of warrants received in connection with the September 30, 2005 securities purchase agreement. Julian Baker and Felix Baker are managing members of Baker Biotech Capital III (Z), L.P. and Baker Biotech Capital II (Z) (GP), LLC, the general partners of Baker Biotech Fund III (Z), L.P., and disclaim beneficial ownership of the shares except to the extent of their pecuniary interest therein.

(8) Includes 50,987 shares of common stock issuable upon exercise of warrants received in connection with the September 30, 2005 securities purchase agreement. Julian Baker and Felix Baker are managing members of Baker Biotech Capital III, L.P. and Baker Biotech Capital II (GP), LLC, the general partners of Baker Biotech Fund III, L.P., and disclaim beneficial ownership of the shares except to the extent of their pecuniary interest therein.

(9) Includes 1,397 shares of common stock issuable upon exercise of warrants received in connection with the September 30, 2005 securities purchase agreement. Julian Baker and Felix Baker are managing members of Baker Biotech Capital, L.P. and Baker Biotech Capital (GP), LLC, the general partners of Baker Bros. Investments II, L.P., and disclaim beneficial ownership of the shares except to the extent of their pecuniary interest therein.

(10) Includes 28,329 shares of common stock issuable upon exercise of warrants received in connection with the September 30, 2005 securities purchase agreement.

(11) BVF Partners, L.P. is the general partner of Biotechnology Value Fund II, Biotechnology Value Fund, L.P., BVF Investments, LLC and Investment 10, LLC. Mark Lampert is the president of BVF, Inc., the general partner of BVF Partners, L.P., and has voting and investment control over the shares owned by Biotechnology Value Fund II, Biotechnology Value Fund, L.P., BVF Investments, LLC and Investment 10, LLC and disclaims beneficiary ownership of such shares except to the extent of his pecuniary interest therein.

(12) Includes 44,730 shares of common stock issuable upon exercise of warrants received in connection with the September 30, 2005 securities purchase agreement.

(13) Includes 68,586 shares of common stock issuable upon exercise of warrants received in connection with the September 30, 2005 securities purchase agreement.

(14) Includes 59,500 shares of common stock issuable upon exercise of warrants received in connection with the September 30, 2005 securities purchase agreement. Capital Ventures International is affiliated with members of the National Association of Securities Dealers, Inc., or NASD, and has represented to us that the shares and warrants held by it were purchased in the ordinary course of business and that at the time of purchase of the shares and warrants held by it, it was not aware of any agreements or understandings, directly or indirectly, with any person to distribute the shares held by it or the common stock issuable upon exercise of the warrants held by it.

(15) Includes 155,246 shares of common stock issuable upon exercise of warrants received in connection with the September 30, 2005 securities purchase agreement.

(16) Includes 143,304 shares of common stock issuable upon exercise of warrants received in connection with the September 30, 2005 securities purchase agreement.

(17) Includes 1,349 shares of common stock issuable upon exercise of warrants received in connection with the September 30, 2005 securities purchase agreement and 2,809 shares of common stock that DLJ Capital Corporation has the right to acquire within 60 days of September 30, 2005 pursuant to the exercise of warrants.

(18) DLJ Capital Corporation and Credit Suisse First Boston Equity, Inc. are wholly owned subsidiaries of Credit Suisse First Boston (USA), Inc., the sole member of Credit Suisse First Boston LLC, a member of the NASD and have represented to us that the shares and warrants held by them were purchased in the ordinary course of business and that at the time of purchase of the shares and warrants held by them, they were not aware of any agreements or understandings, directly or indirectly, with any person to distribute the shares held by them or the common stock issuable upon exercise of the warrants held by them. DLJ Capital Corporation is the managing partner of Sprout Capital IX, L.P., DLJ Associates IX, L.P. is a general partner of Sprout Capital IX, L.P., and Credit Suisse First Boston (USA), Inc. is a limited partner of Sprout Capital IX, L.P. DLJ Capital Corporation is the general partner of Sprout Entrepreneurs Fund, L.P. Credit Suisse First Boston Equity, Inc. wholly owns DLJ LBO Plans Management Corporation II, the general partner of Sprout IX Plan Investors, L.P.

(19) Includes 89,250 shares of common stock issuable upon exercise of warrants received in connection with the September 30, 2005 securities purchase agreement. Nicole Vitullo and Domain Associates, LLC are the managing members of Domain Public Equity Associates, LLC, the sole general partner of Domain Public Equity Partners, L.P. James C. Blair, Brian H. Dovey, Jesse I. Treu, Kathleen K. Schoemaker, Robert J. More and Nicole Vitullo are the managing members of Domain Associates, LLC and share voting and investment control over the shares held by Domain Public Equity Partners, L.P. and disclaim beneficial ownership of such shares except to the extent of their pecuniary interest therein.

(20) Includes 895,650 shares of common stock issuable upon exercise of warrants received in connection with the September 30, 2005 securities purchase agreement. Federated Kaufmann Fund is an affiliate of Federated Investors, a member of the NASD. Federated Kaufmann Fund has represented to us that the shares and warrants held by it were purchased in the ordinary course of business and that at the time of purchase of the shares and warrants held by it, it was not aware of any agreements or understandings, directly or indirectly, with any person to distribute the shares held by it or the common stock issuable upon exercise of the warrants held by it.

(21) Includes 6,824 shares of common stock issuable upon exercise of warrants received in connection with the September 30, 2005 securities purchase agreement and 18,568 shares of common stock that InterWest Investors VII, L.P. has the right to acquire within 60 days of September 30, 2005 pursuant to the exercise of warrants.

(22) Arnold L. Oronsky, a member of our board of directors, is a managing director of InterWest Management Partners VII, LLC, the general partner of InterWest Investors VII, L.P. and InterWest Partners VII, L.P. and, together with the other managing directors and venture members of InterWest Management Partners VII, LLC, has shared voting and investment control over the shares owned by InterWest Investors VII, L.P. and InterWest Partners VII, L.P. Dr. Oronsky and the other managing directors and venture members disclaim beneficial ownership of the shares owned by InterWest Investors VII, L.P. and InterWest Partners VII, L.P. except to the extent of their pecuniary interest therein.

(23) Includes 142,493 shares of common stock issuable upon exercise of warrants received in connection with the September 30, 2005 securities purchase agreement and 387,740 shares of common stock that InterWest Partners VII, L.P. has the right to acquire within 60 days of September 30, 2005 pursuant to the exercise of warrants.

(24) Includes 7,455 shares of common stock issuable upon exercise of warrants received in connection with the September 30, 2005 securities purchase agreement.

(25) Includes 5,950 shares of common stock issuable upon exercise of warrants received in connection with the September 30, 2005 securities purchase agreement. Joseph Klein III, Ms. Sandler's husband, has authorized investment control over the shares owned by Ms. Sandler and also beneficially owns 17,350 shares. Ms. Sandler disclaims any beneficial ownership in shares held by Mr. Klein except to the extent of her pecuniary interest therein.



(26) Includes 88,097 shares of common stock issuable upon exercise of warrants received in connection with the September 30, 2005 securities purchase agreement. Maverick Capital, Ltd., as investment manager of Maverick Fund II, Ltd., has voting and investment control over the shares owned by Maverick Fund II, Ltd. Maverick Capital, Ltd. does not disclaim beneficial ownership of the securities. As of September 30, 2005, Maverick Capital, Ltd. also has voting and investment control over an aggregate of 1,083,886 shares owned by other funds managed by Maverick Capital, Ltd.

(27) Includes 3,795 shares of common stock issuable upon exercise of warrants received in connection with the September 30, 2005 securities purchase agreement and 10,365 shares of common stock that MPM Asset Management Investors 2000 B LLC has the right to acquire within 60 days of September 30, 2005 pursuant to the exercise of warrants.

(28) MPM Capital, L.P. is a direct or indirect parent and/or control person of MPM Asset Management II LLC, funds managed or advised by it (including MPM BioVentures II, L.P., MPM BioVentures II-QP, L.P., MPM BioVentures GmbH & Co. Parallel Beteiligungs KG, and MPM Asset Management Investors 2000 B LLC) and the general partners of such funds, and may be deemed to beneficially hold the shares owned by such entities. Luke B. Evnin, a member of our board of directors, may be deemed to be a control person of MPM Capital, L.P. as a result of his interest in Medical Portfolio Management LLC, the general partner of MPM Capital, L.P. Dr. Evnin disclaims beneficial ownership of such shares except to the extent of his pecuniary interest therein.

(29) Includes 58,037 shares of common stock issuable upon exercise of warrants received in connection with the September 30, 2005 securities purchase agreement and 158,504 shares of common stock that MPM BioVentures GmbH & Co. Parallel Beteiligungs KG has the right to acquire within 60 days of September 30, 2005 pursuant to the exercise of warrants.

(30) Includes 18,195 shares of common stock issuable upon exercise of warrants received in connection with the September 30, 2005 securities purchase agreement and 49,665 shares of common stock that MPM BioVentures II, L.P. has the right to acquire within 60 days of September 30, 2005 pursuant to the exercise of warrants.

(31) Includes 164,854 shares of common stock issuable upon exercise of warrants received in connection with the September 30, 2005 securities purchase agreement and 450,225 shares of common stock that MPM BioVentures II-QP, L.P. has the right to acquire within 60 days of September 30, 2005 pursuant to the exercise of warrants.

(32) Includes 44,825 shares of common stock issuable upon exercise of warrants received in connection with the September 30, 2005 securities purchase agreement.

(33) Matt Zuga is the managing member of Red Abbey Venture Partners, LLC, the general partner of Red Abbey Venture Partners (QP), L.P., Red Abbey Venture Partners, L.P. and Red Abbey CEO's Fund, L.P., and disclaims any beneficial ownership of the shares except to the extent of his pecuniary interest therein.

(34) Includes 12,471 shares of common stock issuable upon exercise of warrants received in connection with the September 30, 2005 securities purchase agreement.

(35) Includes 2,431 shares of common stock issuable upon exercise of warrants received in connection with the September 30, 2005 securities purchase agreement.

(36) Includes 11,935 shares of common stock issuable upon exercise of warrants received in connection with the September 30, 2005 securities purchase agreement.

(37) David Greenhouse and Austin Marx are the principal owners of MGP Limited Partnership, a general partner and investment advisor to Special Situations Fund III, L.P., AWM Investment Company, Inc., the general partner of MGP Limited Partnership and the general partner and investment advisor to Special

Situations Cayman Fund L.P., and MG Advisers LLC, the general partner and investment advisor to Special Situations Private Equity Fund L.P. Mr. Greenhouse and Mr. Marx disclaim beneficial ownership of the shares held by Special Situations Fund III, L.P., Special Situations Cayman Fund L.P. and Special Situations Private Equity Fund L.P. except to the extent of their pecuniary interest therein.

(38) Includes 47,740 shares of common stock issuable upon exercise of warrants received in connection with the September 30, 2005 securities purchase agreement.

(39) Includes 59,675 shares of common stock issuable upon exercise of warrants received in connection with the September 30, 2005 securities purchase agreement.

(40) Includes 112,525 shares of common stock issuable upon exercise of warrants received in connection with the September 30, 2005 securities purchase agreement and 231,789 shares of common stock that Sprout Capital IX, L.P. has the right to acquire within 60 days of September 30, 2005 pursuant to the exercise of warrants.

(41) Includes 443 shares of common stock issuable upon exercise of warrants received in connection with the September 30, 2005 securities purchase agreement and 913 shares of common stock that Sprout Entrepreneurs Fund, L.P. has the right to acquire within 60 days of September 30, 2005 pursuant to the exercise of warrants.

(42) Includes 5,137 shares of common stock issuable upon exercise of warrants received in connection with the September 30, 2005 securities purchase agreement and 13,380 shares of common stock that Sprout IX Plan Investors, L.P. has the right to acquire within 60 days of September 30, 2005 pursuant to the exercise of warrants.

(43) Includes 59,500 shares of common stock issuable upon exercise of warrants received in connection with the September 30, 2005 securities purchase agreement. Kevin C. Tang has voting and investment control over the shares owned by Tang Capital Partners and disclaims beneficial ownership of such shares except to the extent of his pecuniary interest therein.

### PLAN OF DISTRIBUTION

The selling stockholders, which as used herein includes donees, pledgees, transferees or other successors-in-interest selling shares of common stock or interests in shares of common stock received after the date of this prospectus from a selling stockholder as a gift, pledge, partnership distribution or other transfer, may, from time to time, sell, transfer or otherwise dispose of any or all of their shares of common stock or interests in shares of common stock on any stock exchange, automated interdealer quotation system, market or trading facility on which the shares are traded, in the over-the-counter market, or in private transactions. These dispositions may be at fixed prices that may be changed, at market prices prevailing at the time of sale, at prices related to prevailing market prices, at varying prices determined at the time of sale or at prices otherwise negotiated. The selling stockholders will act independently of us in making decisions with respect to the timing, manner and size of each sale. The selling stockholders may sell the securities using one or more, or a combination of the following methods:

on The Nasdaq National Market (or any other exchange or automated quotation system on which the shares may be listed),

on the over-the-counter market,

ordinary brokerage transactions and transactions in which the broker-dealer solicits purchasers,

block trades in which the broker-dealer will attempt to sell the shares as agent, but may position and resell a portion of the block as principal to facilitate the transaction,

purchases by a broker-dealer as principal and resale by the broker or dealer for its account,

an exchange distribution in accordance with the rules of the applicable exchange,

privately negotiated transactions,

short sales,

through the writing or settlement of options or other hedging transactions, whether through an options exchange or otherwise,

through the distribution of the common stock by any selling stockholders to its partners, members or stockholders,

through one or more underwritten offerings on a firm commitment or best efforts basis,

broker-dealers may agree with the selling stockholders to sell a specified number of such shares at a stipulated price per share,

a combination of any such methods of sale, and

any other method permitted pursuant to applicable law.

In addition, any shares that qualify for sale pursuant to Rule 144 promulgated under the Securities Act may be sold under Rule 144 rather than pursuant to this prospectus.

The selling stockholders may, from time to time, pledge or grant a security interest in some or all of the shares of common stock owned by them and, if they default in the performance of their secured obligations, the pledgees or secured parties may offer and sell the shares of common stock, from time to time, under this prospectus, or under a supplement to this prospectus under Rule 424(b) or under any applicable provision of the Securities Act amending the list of selling stockholders to include the pledgee, transferee or other successors-in-interest as selling

stockholders under this prospectus. The selling stockholders also may transfer the shares of common stock in other circumstances, in which case the transferees, pledgees or other successors in interest will be the selling beneficial owners for purposes of this prospectus. To the extent required, this prospectus may be amended or supplemented from time to time to describe a specific plan of distribution.

In connection with distributions of the shares of our common stock or interests therein, the selling stockholders may enter into hedging transactions with broker-dealers or other financial institutions, which institutions may, in turn, engage in short sales of shares of our common stock in the course of hedging the positions they assume with the selling stockholders. The selling stockholders may also sell the shares of our common stock short and redeliver these shares to close out the selling stockholders' short positions, or loan or pledge shares of our common stock to broker-dealers that may in turn sell these securities. The selling stockholders may also enter into option or other transactions with broker-dealers or other financial institutions or the creation of one or more derivative securities which require the delivery to such broker-dealer or other financial institution of shares of our common stock offered by this prospectus, which shares such broker-dealer or other financial institution may resell pursuant to this prospectus (as supplemented or amended to reflect such transaction).

The aggregate proceeds to the selling stockholders from the sale of the shares of common stock offered by them will be the purchase price of the shares less discounts or commissions, if any. Each of the selling stockholders reserves the right to accept and, together with their agents from time to time, to reject, in whole or in part, any proposed purchase of common stock to be made directly or through agents. We will not receive any of the proceeds from this offering. Upon any exercise of the warrants by payment of cash, however, we will receive the exercise price of the warrants. The warrants are also exercisable on a cashless basis. We will not receive any cash payment from the selling stockholders upon any exercise of the warrants on a cashless basis.

The selling stockholders may engage brokers and dealers, and any brokers or dealers may arrange for other brokers or dealers to participate in effecting sales of the securities. These brokers, dealers or underwriters may act as principals, or as an agent of a selling securityholder. Broker-dealers may agree with a selling stockholder to sell a specified number of the securities at a stipulated price per security. If the broker-dealer is unable to sell securities acting as agent for a selling stockholder, it may purchase as principal any unsold securities at the stipulated price. Broker-dealers who acquire securities as principals may thereafter resell the securities from time to time in transactions in any stock exchange or automated interdealer quotation system on which the securities are then listed, at prices and on terms then prevailing at the time of sale, at prices related to the then-current market price or in negotiated transactions. Broker-dealers may use block transactions and sales to and through broker-dealers, including transactions of the nature described above.

To the extent required under the Securities Act, the aggregate amount of selling stockholders' securities being offered and the terms of the offering, the names of any agents, brokers, dealers or underwriters and any applicable commission with respect to a particular offer will be set forth in an accompanying prospectus supplement. Any underwriters, dealers, brokers or agents participating in the distribution of the securities may receive compensation in the form of underwriting discounts, concessions, commissions or fees from a selling stockholder and/or purchasers of selling stockholders' securities of securities, for whom they may act (which compensation as to a particular broker-dealer might be in excess of customary commissions).

The selling stockholders and any underwriters, broker-dealers or agents that participate in the sale of the shares of common stock or interests therein may be underwriters within the meaning of Section 2(11) of the Securities Act. Any discounts, commissions, concessions or profit they earn on any resale of the shares may be underwriting discounts and commissions under the Securities Act. Selling stockholders who are underwriters within the meaning of Section 2(11) of the Securities Act will be subject to the prospectus delivery requirements of the Securities Act. The selling stockholders may indemnify any broker-dealer that participates in transactions involving the sale of the shares against certain liabilities, including liabilities arising under the Securities Act.

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We will bear substantially all of the costs, expenses and fees in connection with the registration of the shares of common stock, other than any commissions, discounts or other fees payable to broker-dealers in connection with any sale of shares, which will be borne by the selling stockholder selling such shares of common stock. We have agreed to indemnify the selling stockholders against certain liabilities, including liabilities under the Securities Act and state securities laws, relating to the registration of the shares offered by this prospectus.

In order to comply with the securities laws of some states, if applicable, the shares of common stock may be sold in these jurisdictions only through registered or licensed brokers or dealers. In addition, in some states the shares may not be sold unless they have been registered or qualified for sale or an exemption from registration or qualification requirements is available and is complied with.

We have advised the selling stockholders that the anti-manipulation rules of Regulation M under the Exchange Act may apply to sales of shares of our common stock in the market and to the activities of the selling stockholders. These rules may limit the timing of purchases and sales of the shares by such selling stockholders.

We will make copies of this prospectus (as it may be supplemented or amended from time to time) available to the selling stockholders for the purpose of satisfying the prospectus delivery requirements of the Securities Act.

We have agreed with each selling stockholder to keep the registration statement of which this prospectus constitutes a part effective with respect to its shares of our common stock until the earlier of (1) September 30, 2007, (2) the date on which all shares purchased from us, or issuable upon exercise of warrants purchased from us, by such selling stockholders in the private placement may be resold during any 90-day period pursuant to Rule 144 of the Securities Act, or (3) the date on which all shares purchased from us, or acquirable upon exercise of warrants purchased from us, by such selling stockholders have been resold.

## LEGAL MATTERS

The validity of the shares of common stock being offered by this prospectus will be passed upon for us by Cooley Godward LLP, San Diego, California. As of the date of this prospectus, investment funds affiliated with Cooley Godward LLP owned 22,371 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, have audited our financial statements included in our Annual Report on Form 10-K for the year ended December 31, 2004, 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 are subject to the informational requirements of the Exchange Act and in accordance therewith, file reports, proxy statements and other information with the Securities and Exchange Commission. Such reports, proxy statements and other information filed by us may be inspected and copied at the Security and Exchange Commission's Public Reference Section located at 100 F Street, N.E., Washington, D.C. 20549. Copies of such material also can be obtained from the Public Reference Section of the Commission at 100 F Street, N.E., Washington, D.C. 20549, at prescribed rates. Please call the Securities and Exchange Commission at 1-800-SEC-0330 for more information about the operation of the



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public reference rooms. The Securities and Exchange Commission also makes electronic filings publicly available on the Internet. The Securities and Exchange Commission's Internet address is <http://www.sec.gov>. The Securities and Exchange Commission's website also contains reports, proxy and information statements and other information regarding us that has been filed with the Securities and Exchange Commission. Our common stock is quoted on The Nasdaq National Market. Reports, proxy statements and other information concerning us may be inspected at the National Association of Securities Dealers, Inc. at 1735 K Street, N.W., Washington, D.C. 20006.

This prospectus constitutes a part of a registration statement on Form S-3 filed by us with the Securities and Exchange Commission under the Securities Act, including amendments thereto relating to the common stock offered hereby. This prospectus does not contain all of the information set forth in the registration statement.

The Securities and Exchange Commission allows us to incorporate by reference information that we file with them, which means that we can disclose important information to you by referring you to those documents. The information incorporated by reference is an important part of this prospectus, and information that we file later with the Securities and Exchange Commission will automatically update and supersede this information. Further, all filings we make under the Exchange Act after the date of the initial registration statement and prior to effectiveness of the registration statement shall be deemed to be incorporated by reference into this prospectus. We incorporate by reference the documents listed below and any future filings we will make with the Securities and Exchange Commission under Section 13(a), 13(c), 14 or 15(d) of the Exchange Act:

- (i) Our Annual Report on Form 10-K for the year ended December 31, 2004, including all material incorporated by reference therein,
- (ii) Our Quarterly Reports on Form 10-Q for the quarters ended March 31, 2005 and June 30, 2005,
- (iii) Our Current Reports on Form 8-K filed on January 25, 2005, March 17, 2005, June 27, 2005 and October 5, 2005, and
- (iv) 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, CA 92037, (858) 587-2770.