METABASIS THERAPEUTICS INC
Form S-3
May 09, 2008

As filed with the Securities and Exchange Commission on May 9, 2008

Registration No. 333-

UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM S-3

REGISTRATION STATEMENT

UNDER

THE SECURITIES ACT OF 1933

METABASIS THERAPEUTICS, INC.

(Exact name of registrant as specified in its charter)

Delaware	**33-0753322**
(State or other jurisdiction of incorporation or organization)	(I.R.S. Employer Identification Number)

11119 North Torrey Pines Road

La Jolla, CA 92037

(858) 587-2770

(Address, including zip code, and telephone number, including

area code, of registrant s principal executive offices)

Paul K. Laikind, Ph.D.

President and Chief Executive Officer

Metabasis Therapeutics, Inc.

11119 North Torrey Pines Road

La Jolla, CA 92037

(858) 587-2770

(Name, address, including zip code, and telephone number, including

area code, of agent for service)

Copies to:

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San Diego, CA 92121

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Approximate date of commencement of proposed sale to the public: As soon as practicable after the effective date of this registration statement.

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

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

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

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

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

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

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or a smaller reporting company. See definition of large accelerated filer, accelerated filer and smaller reporting company in Rule 12b-2 of the Exchange Act. (check one):

Large accelerated filer o	Accelerated filer x
Non-accelerated filer o (Do not check if a smaller reporting company)	Smaller reporting company o

CALCULATION OF REGISTRATION FEE

Title of each class of securities to be registered	Amount to be registered (1)	Proposed maximum offering price per share (2)	Proposed maximum aggregate offering price (2)	Amount of registration fee (3)
Common Stock, $0.001 par value per share	4,170,939 shares	$ 2.31	$ 9,634,869.09	$ 379
Common Stock, $0.001 par value per share, issuable upon the exercise of warrants	1,057,196 shares	$ 2.31	$ 2,442,122.76	$ 96

Total	5,228,135 shares	$ 2.31	$ 12,076,991.85	$ 475

(1) Based upon the estimated maximum number of shares of common stock that may be sold by the selling stockholders. Pursuant to Rule 416(a) under the Securities Act this registration statement also registers such additional shares of the registrant s common stock as may hereafter be offered or issued to prevent dilution resulting from stock splits, stock dividends, recapitalizations or certain other capital adjustments.

(2) Estimated solely for the purpose of computing the amount of the registration fee pursuant to Rule 457(c) of the Securities Act. The price per share and aggregate offering price are based upon the average of the high and low sales prices of the Registrant s common stock on May 6, 2008, as reported on the Nasdaq Stock Market.

(3) Calculated by multiplying $39.30 by the proposed maximum aggregate offering price.

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

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

SUBJECT TO COMPLETION, DATED MAY 9, 2008

PRELIMINARY PROSPECTUS

5,228,135 Shares

Common Stock

This prospectus relates to the offer and sale, from time to time, of up to 5,228,135 shares of Metabasis Therapeutics, Inc. common stock held by the selling stockholders listed on page 28 of this prospectus, including common stock issuable upon exercise of warrants. The selling stockholders purchased the common stock and warrants to purchase common stock from us in our April 2008 warrant exchange and concurrent private placement. 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 Stock Market under the symbol MBRX. On May 8, 2008, the last reported sale price for our common stock was $2.09 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 3 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 , 2008.

Table of Contents

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 discovering, developing and commercializing novel drugs by applying our proprietary technologies, scientific expertise and unique capabilities for targeting the liver and liver pathways. We have established a broad pipeline of product candidates and advanced research programs targeting large markets with significant unmet needs. Our product pipeline includes product candidates and advanced research programs for the treatment of metabolic diseases such as diabetes and hyperlipidemia, which we refer to as our core assets, as well as product candidates and advanced research programs for the treatment of liver diseases such as hepatitis and primary liver cancer, which we refer to as our non-core assets. All of our product candidates were developed internally using our proprietary technologies.

We currently have four product candidates at the clinical stage of development. These product candidates include our core metabolic disease product candidates, MB07803 and MB07811, which are being developed as potential treatments for type 2 diabetes and hyperlipidemia, respectively, and our non-core liver disease product candidates, pradefovir and MB07133, which have been developed as potential treatments for hepatitis B and primary liver cancer, respectively.

Under our strategic plan we will focus our internal resources primarily on our clinical and advanced research core metabolic disease programs. This includes funding the further clinical evaluation of our core assets, MB07803 and MB07811, with a focus on achieving key milestones. Continued development of these core assets thereafter will require significant resources. Therefore, we plan to establish strategic collaborations for these core assets at appropriate times to secure additional resources, accelerate progress and share risk. In addition, we plan to advance additional metabolic disease product candidates discovered by our research group into clinical development either independently, or potentially with current or future strategic collaborators.

In order to reduce future expenses and to minimize the potential dilution associated with financing internal development, we intend to license pradefovir and MB07133 for further development and commercialization.

We currently do not have strategic collaborations in place related to our core assets, MB07803 or MB07811, and we intend to license our non-core assets, pradefovir and MB07133. We retain worldwide commercialization rights to all of the compounds that we have generated from our past and current research programs, with the exception of any potential future product candidates covered by our collaborations with Merck & Co., Inc., or Merck, and Idenix Pharmaceuticals, Inc., or Idenix. Our potential future agreements with strategic collaborators may include joint marketing or promotion arrangements which may allow us to eventually co-market one or more of our product candidates through

our own sales force or with a co-promotion partner. Alternatively, we may grant exclusive marketing rights to our collaborators in exchange for up-front fees, milestones and royalties on future sales, if any.

We were incorporated in Delaware in April 1997 as a wholly owned subsidiary of Gensia Sicor Inc., now Sicor Inc., which became an indirect wholly owned subsidiary of Teva Pharmaceutical Industries Limited in January 2004. In December 1997, Sicor assigned to us specified assets and liabilities relating to its then existing business of discovering and developing proprietary pharmaceutical products. Although we established a new business plan, pursued new opportunities and discovered new products and technologies following our inception, many of the assets we obtained in the transfer served as a foundation upon which we built our technologies and know how. In June 1999 we completed a corporate restructuring and management stock purchase in which we became an

independent company. We have a wholly owned subsidiary, Aramed, Inc., which was transferred to us by Sicor and does not conduct an active business.

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

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 and in our other filings with the Securities and Exchange Commission, 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 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 core metabolic disease assets, MB07803 and MB07811, and our non-core liver disease assets, pradefovir and MB07133. Clinical trials conducted to date have provided initial evidence of safety with all of our product candidates and initial evidence of efficacy in certain of our product candidates. However, to date, no pivotal, adequate and well-controlled clinical trials designed to provide clinical and statistically significant proof of efficacy, or to provide sufficient evidence of safety to justify approval, have been completed with any of our product candidates. All of our product candidates will require additional development, including clinical trials as well as further animal studies to evaluate their toxicology, carcinogenicity and pharmacokinetics and optimize their formulation, and regulatory clearances before they can be commercialized. Positive results obtained during early development do not necessarily mean later development will succeed or that regulatory clearances will be obtained. Our product development efforts may not lead to commercial drugs, either because our product candidates fail to be safe and effective or because we have inadequate financial or other resources to pursue our product candidates through the clinical development and approval processes. If any of our product candidates fail to demonstrate safety or efficacy at any time or during any phase of development, we would experience potentially significant delays in, or be required to abandon, development of the product candidate.

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

If development of our product candidates does not produce favorable results, we and our collaborators, as applicable, may be unable to commercialize these products.

To receive regulatory approval for the commercialization of our core metabolic disease assets, MB07803 and MB07811, our non-core liver disease assets, pradefovir and 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 Food and Drug Administration, or FDA, in the U.S. and other regulatory agencies elsewhere in the world. In order to support marketing approval, these agencies typically require successful results in

one or more Phase 3 clinical trials, which our current product candidates have not yet reached and may never reach. In addition, regulatory approval of our product candidates may be affected by adverse results in animal studies conducted during clinical development to, among other things, evaluate their toxicology, carcinogenicity and pharmacokinetics and optimize their formulation.

The development process is expensive, can take many years and has an uncertain outcome. Failure can occur at any stage of the process. We may experience numerous unforeseen events during, or as a result of, the development

process that could delay or prevent commercialization of our current or future product candidates, including the following:

- clinical trials may produce negative or inconclusive results,

- animal studies conducted on product candidates during clinical development to, among other things, evaluate their toxicology and pharmacokinetics and optimize their formulation may produce unfavorable results,

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

- costs of development 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 development of our product candidates may not devote sufficient resources to these clinical trials or other studies of these candidates or conduct them in a timely manner, or

- we may face delays in obtaining regulatory approvals to commence a clinical trial.

Success in early development does not mean that later development will be successful because, for example, product candidates in later-stage clinical trials may fail to demonstrate sufficient safety and efficacy despite having progressed through initial clinical testing. For example, in July 2007, we were informed by Daiichi Sankyo, our collaborative partner on CS-917, that results from a completed Phase 2b clinical trial showed that this product candidate failed to achieve the primary endpoint of the clinical trial despite having successfully achieved the primary endpoints of other earlier clinical trials. In January 2008, we and Daiichi Sankyo agreed to terminate our strategic collaboration on CS-917 and return the rights to this product candidate to us. We do not intend to further develop this product candidate.

Our clinical experience with our product candidates is limited, and to date our product candidates have been tested in less than the number of patients that will likely need to be studied to gain regulatory approval. The data collected from clinical trials with larger patient populations may not demonstrate sufficient safety and efficacy to support regulatory approval of these product candidates. In addition, the requirements for regulatory approval of our product candidates may change, making it more difficult for us to achieve such approval in a timely manner or at all. For example, in March 2008 the FDA released draft guidance regarding clinical trials for product candidates that treat diabetes, which may result in more stringent requirements for the clinical testing and regulatory approval of such product candidates.

We currently do not have strategic collaborations in place for any of our current product candidates. Therefore, in the future, we and/or any potential future collaborative partner will be responsible for establishing the targeted endpoints and goals for development of our product candidates. These targeted endpoints and goals may be inadequate to demonstrate the safety and efficacy levels required for regulatory approvals. Even if we believe data collected during the development 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, data generated during development 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.

We may not be able to enter into collaborations with respect to our non-core assets, pradefovir and MB07133, and certain metabolic disease advanced research programs on acceptable terms, if at all, which would lead to development and commercialization delays.

Since we do not currently possess the resources necessary to independently develop and commercialize all of the potential product candidates that may be based upon our technologies, including MB07803, MB07811, pradefovir and MB07133, and as a component of our strategic plan, we plan to enter into additional collaborative agreements to assist in the development and commercialization of some or all of these product candidates. However, our discussions with potential collaborators may not lead to the establishment of new collaborations on acceptable terms, if at all, or it may take longer than expected to establish new collaborations, leading to development and commercialization delays, which would adversely affect our business.

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 observed in human clinical trials or in supportive animal studies with our product candidates could interrupt, delay or halt their development and could result in the denial of regulatory approval by the FDA or other regulatory authorities for any or all targeted indications or adversely affect the marketability of any such product candidates that receive regulatory approval. In turn, this could eliminate or limit our ability to commercialize our product candidates and generate revenues from their sale.

For example, data from 24-month oral carcinogenicity studies of pradefovir in rats and mice showed that the incidence of rats or mice with tumors was increased in the animals dosed with the highest dose levels tested and was slightly increased at the intermediate dose levels. The low dose levels were considered no-effect dose levels in both studies. As a result of numerous factors which may include these findings, we entered into an agreement with Schering and Valeant Pharmaceuticals North America, or Valeant, to terminate our agreements for the development and commercialization of pradefovir, and all commercial rights to pradefovir have been returned to us subject to certain milestone and royalty payments we may be required to make to Valeant should pradefovir be subsequently developed.

Our product candidates could also exhibit adverse interactions with other drugs. For example, in earlier clinical trials conducted by Daiichi Sankyo, CS-917 was associated with incidents of lactic acidosis in two patients when it was combined with metformin in a Phase 1 clinical trial. After extensive analysis, Daiichi Sankyo concluded that these incidents were likely due to significantly increased blood levels of metformin. CS-917 was also associated in a limited number of patients with episodes of hypoglycemia, asymptomatic lactate elevation as well as lactate elevation with clinical symptoms that could be considered signs of lactic acidosis. We are currently conducting clinical trials of our second-generation product candidate for type 2 diabetes, MB07803, which works by the same mechanism as CS-917 and thus may be subject to some or all of the same risks as CS-917. To date, no incidents of lacticemia, lactic acidosis, hypoglycemia or other significant adverse side effects have been observed in clinical trials of MB07803.

The unique nature of our proprietary technologies including HepDirect and NuMimetic may cause undesirable side effects in future clinical trials or supportive animal studies. In addition, our product candidates may have greater or lesser degrees of potential risk of undesirable side effects relative to other product candidates based on the nature of their molecular targets and the various physiological responses associated with those targets. For example, MB07811 is a product candidate designed to exploit the beneficial hepatic effects of thyroid hormone agonists while avoiding toxicities related to systemic exposure to these types of compounds. If MB07811 is not successful in this regard, it could be associated with undesirable side effects.

Undesirable side effects involving our product candidates may have other significant adverse implications on our business, for example:

- we may be unable to obtain additional financing on acceptable terms, if at all,

- our stock price could decline,

- our collaborators may ultimately terminate development of our partnered products, may further decide not to develop backup product candidates and may terminate our agreements,

- if these agreements were terminated we may determine not to further develop the affected product candidates due to resource constraints and may not be able to establish additional collaborations for their further development on acceptable terms, if at all,

- if we were to later continue the development of these product candidates and receive regulatory approval, earlier findings may significantly limit their marketability and thus significantly lower our potential future revenues from their sale,

- we may be subject to product liability or stockholder litigation, and

- we may be unable to attract and retain key employees.

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

- regulatory authorities may withdraw their approval of the product, or we may decide to cease marketing and sale of the product voluntarily,

- we may be required to change the way the product is administered, conduct additional studies, change the labeling of the product, or change the product s manufacturing facilities, and

- our reputation may suffer.

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

We are currently dependent on our collaborations with Merck and Idenix for the development and commercialization of product candidates related to those collaborations, and we may be dependent on future collaborators for the development of our current and future product candidates. Events involving our collaborations with Merck and Idenix, or any future collaborations could prevent us from developing and commercializing our product candidates and achieving or sustaining profitability.

We have entered into two collaborations with Merck and a collaboration with Idenix. The first collaboration with Merck seeks to develop and commercialize new products for the treatment of hepatitis C infection and the second seeks to develop and commercialize new products to treat type 2 diabetes and potentially other metabolic diseases. Our collaboration with Idenix seeks to develop and commercialize new products for the treatment of hepatitis C infection. Although our collaborations with Merck and Idenix have not yet yielded any product candidates, should they ultimately be successful, we will be dependent on Merck and/or Idenix, as applicable, for further development and commercialization of any resulting product candidates. In October 2007, the sponsored research term of our collaboration agreement with Idenix was ended upon the first anniversary of the agreement in accordance with its terms. While the sponsored research portion of our collaboration with Idenix ended, certain compounds are under evaluation for further development.

We have limited control over the amount and timing of resources that Merck, Idenix or any future collaborators devote to our programs or potential product candidates. These collaborations with us may end or may be terminated or our collaborators may otherwise fail to conduct their collaborative activities successfully and in a timely manner. Further, our collaborators may not develop product candidates that arise out of our collaborative arrangements or devote sufficient resources to the development, manufacture, marketing or sale of these products. In the event that one of our collaborations is terminated, and we believe that the continued development or commercialization of a product candidate or drug compound covered by the collaboration is warranted, we may seek to obtain rights to develop and commercialize the product candidate or drug compound, if we do 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. For example, at this time, we do not intend to independently develop pradefovir or MB07133 and intend to license these product candidates for further development and commercialization.

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,

- our product candidates do not meet the primary endpoints of any clinical trials conducted on them or exhibit undesirable side effects,

- 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 and Idenix may involve Merck s or Idenix s proprietary compounds, if Merck or Idenix terminate development of product candidates we may not have the right to pursue development of these product candidates on our own.

The objective of our hepatitis C collaboration with Merck has been to discover product candidates for the treatment of this disease by applying our technology to certain compounds provided by Merck.

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

Our agreement with Merck to develop and commercialize new products to treat type 2 diabetes and potentially other metabolic diseases may include the development of compounds owned or controlled by Merck. Accordingly, if Merck terminates this collaboration, it may prove difficult for us to continue development of such compounds. Similarly, our agreement with Idenix to develop and commercialize new products to treat hepatitis C infection may include the development of compounds owned or controlled by Idenix. In October 2007, the sponsored research term of our collaboration agreement with Idenix ended upon the first anniversary of the agreement in accordance with its terms. While the sponsored research portion of our collaboration with Idenix ended, certain compounds are under evaluation for further development. Idenix may not choose to develop the compounds discovered during the research term, should it do so and then decide to terminate this collaboration, it may prove difficult for us to continue development of such compounds.

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

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

- unwillingness on the part of a collaborator to pay us research funding, milestone payments or royalties we believe are due to us under our collaboration agreement,

- uncertainty regarding ownership of intellectual property rights arising from our collaborative activities, which could prevent us from entering into additional collaborations or independently pursuing the development and/or commercialization of product candidates, or disagreements with our collaborators regarding the protection of intellectual property rights,

- unwillingness on the part of a collaborator to keep us informed regarding the progress of its development and commercialization activities or to permit public disclosure of the results of those activities, or

- slowing or cessation of a collaborator s development or commercialization efforts with respect to our product candidates.

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

We intend to use our proprietary technologies and our knowledge and expertise to develop and commercialize novel drugs to address some of the world s most widespread and costly chronic diseases. Our goal is to expand our core metabolic disease clinical development pipeline by

continuing to develop and move additional new drug compounds into clinical development. However, the process of researching and discovering drug compounds is expensive, time-consuming and unpredictable. Data from our current research programs may not support the clinical development of our lead compounds or other compounds from these programs, and we may not identify any additional drug compounds suitable for recommendation for clinical development. Moreover, any drug compounds we recommend for clinical development may not demonstrate, through preclinical testing, indications of safety and potential efficacy, that such drug compounds warrant advancement into clinical trials. Such findings would potentially impede our ability to maintain or expand our clinical development pipeline. Our ability to identify new drug compounds and advance them into clinical development also depends upon our ability to fund our research and development operations, and we cannot be certain that additional funding will be available on acceptable terms, or at all.

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

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

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

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

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

- unforeseen safety issues, or

- lack of adequate funding to continue the clinical trial.

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

We rely on third parties in connection with the devel