METABASIS THERAPEUTICS INC
Form 10-K
March 23, 2006

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

WASHINGTON, DC 20549

Form 10-K

FOR ANNUAL AND TRANSITION REPORTS
PURSUANT TO SECTIONS 13 OR 15(d)
OF THE SECURITIES EXCHANGE ACT OF 1934

(Mark One)

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

For the fiscal year ended December 31, 2005

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

For the transition period from to

Commission file number: 000-50785

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 No.)
11119 North Torrey Pines Road, La Jolla, CA	**92037**
(Address of principal executive offices)	(Zip Code)

(858) 587-2770

(Registrant s telephone number, including area code)

Securities registered pursuant to Section 12(b) of the Act:

Title of Each Class	Name of Each Exchange on Which Registered
None	None

Securities registered pursuant to Section 12(g) of the Act:

Common Stock, par value $0.001 per share

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

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

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

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

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

Large accelerated filer o Accelerated filer o Non-accelerated filer ý

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

As of June 30, 2005, the last business day of the registrant s most recently completed second fiscal quarter, the aggregate market value of the registrant s common stock held by non-affiliates of the registrant was approximately $16.0 million, based on the closing price of the registrant s common stock on the Nasdaq National Market on June 30, 2005 of $3.15 per share. Shares of common stock held by executive officers, directors and 10% or greater stockholders of the registrant have been excluded in that such persons or entities may be deemed to be affiliates. This determination of affiliate status is not necessarily a conclusive determination for other purposes.

The number of outstanding shares of the registrant s common stock, par value $0.001 per share, as of March 1, 2006 was 25,325,605.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant s definitive Proxy Statement to be filed with the Securities and Exchange Commission within 120 days after the end of the registrant s fiscal year ended December 31, 2005 are incorporated by reference into Part III of this report.

METABASIS THERAPEUTICS, INC.

FORM 10-K ANNUAL REPORT

FOR THE YEAR ENDED DECEMBER 31, 2005

TABLE OF CONTENTS

PART I	
Item 1	Business
Item 1A	Risk Factors
Item 1B	Unresolved Staff Comments
Item 2	Properties
Item 3	Legal Proceedings
Item 4	Submission of Matters to a Vote of Security Holders
PART II	
Item 5	Market for Registrant s Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities
Item 6	Selected Financial Data
Item 7	Management s Discussion and Analysis of Financial Condition and Results of Operations
Item 7A	Quantitative and Qualitative Disclosures About Market Risk
Item 8	Financial Statements and Supplementary Data
Item 9	Changes in and Disagreements With Accountants on Accounting and Financial Disclosures
Item 9A	Controls and Procedures
Item 9B	Other Information
PART III	
Item 10	Directors and Executive Officers of the Registrant
Item 11	Executive Compensation
Item 12	Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters
Item 13	Certain Relationships and Related Transactions
Item 14	Principal Accountant Fees and Services
PART IV	
Item 15	Exhibits and Financial Statement Schedules
SIGNATURES	

PART I

Item 1. Business

Forward-Looking Statements

This annual report on Form 10-K contains 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, potential, predicts, projects, 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 the Risk Factors section below and in our other filings with the Securities and Exchange Commission. Our actual results may differ materially from those anticipated in these forward-looking statements. Readers are cautioned not to place undue reliance on forward-looking statements. The forward-looking statements speak only as of the date on which they are made, and we undertake no obligation to update such statements to reflect events that occur or circumstances that exist after the date on which they are made.

Overview

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

We currently have the following four product candidates in clinical trials in descending order from our most advanced product, pradefovir:

Pradefovir, a product candidate for the treatment of hepatitis B that has successfully completed Phase II clinical trials and is scheduled to enter Phase III clinical trials in 2006. Pradefovir uses our HepDirect technology to target the active form of Hepsera, a marketed anti-viral drug indicated for the treatment of hepatitis B, selectively to the liver. The active form of Hepsera is known as adefovir. Hepsera delivers adefovir throughout the body, rather than selectively to the liver. We believe that Hepsera, which is indicated for the treatment of hepatitis B, is used at a suboptimal dose due to an increased risk of kidney toxicity at higher doses. Because pradefovir targets adefovir to the liver while limiting the amount that reaches other organs, we believe that higher liver levels of the active drug may be

achieved without causing kidney toxicity, thereby providing greater efficacy. In July 2004 Valeant Pharmaceuticals International, with whom we are collaborating with respect to the development of pradefovir and to whom we have licensed worldwide commercialization rights, commenced a 48 week dose-ranging Phase II clinical trial of pradefovir, the purpose of which was to evaluate safety and efficacy and select an appropriate dose for potential Phase III clinical trials. Based on the decision to initiate this Phase II clinical trial, we earned a $1 million milestone payment from Valeant. In the clinical trial, which was completed in 2005 and met its primary efficacy end-point, Valeant reported that pradefovir produced greater viral load reductions than Hepsera and was safe and well tolerated with no evidence of renal toxicity. Based on the promising results seen in the Phase II clinical trial and after discussions with the U.S. Food and Drug Administration, or FDA, Valeant has informed us that it intends to initiate the Phase III clinical trials for pradefovir in 2006. (Pradefovir was formerly called remofovir and before that, Hepavir B.)

CS-917, a product candidate for the treatment of type 2 diabetes that is currently in Phase II clinical trials. CS-917 is being developed in collaboration with Daiichi Sankyo Co., Ltd. In addition to having responsibility for clinical development of the drug, Daiichi Sankyo has worldwide commercialization rights. We have retained co-promotion rights for CS-917 in North America. We believe CS-917, which we discovered using our NuMimetic

technology, inhibits a metabolic pathway in the liver that is responsible for producing the sugar called glucose. In type 2 diabetic patients, this pathway produces excessive amounts of glucose, a process that contributes to high blood glucose levels which in turn may lead to morbidity and death. Daiichi Sankyo reports that results from a 14-day Phase II clinical trial and a 28-day Phase II clinical trial, both in type 2 diabetic subjects, demonstrated that CS-917 is capable of significantly lowering blood glucose levels. Based on the results of the 28-day clinical trial, we earned a $3.5 million milestone payment from Daiichi Sankyo. CS-917 is currently in a Phase IIb clinical trial designed to allow measurement of the regulatory endpoint hemoglobin A1c, a standard measure of long-term glucose control, after 3 months of dosing.

MB07133, a product candidate for the treatment of primary liver cancer that is currently in a Phase I/II clinical trial designed to evaluate safety and preliminary efficacy in a limited number of patients. MB07133 uses our HepDirect technology to target the active form of araC to the liver while decreasing levels of the active form of the drug in tissues outside of the liver. AraC is a marketed anti cancer drug used to treat leukemia. We believe MB07133 s unique liver-targeting property will enhance efficacy in the liver while minimizing the toxicities associated with araC therapy. MB07133 is currently being studied in patients with primary liver cancer to identify the maximum tolerated dose. Once this dose is identified, we plan to study MB07133 at that dose in a limited number of patients in order to evaluate its potential efficacy. We retain all rights to MB07133.

MB07803, a product candidate for the treatment of type 2 diabetes that is currently in a Phase I clinical trial. We consider MB078703 to be a second generation inhibitor of the metabolic pathway in the liver that is responsible for producing glucose and is designed to work by the same mechanism as CS-917. In early 2006 we began a Phase I clinical trial with MB07083 to assess its safety in healthy human volunteers. We retain all rights to MB07803.

In addition to these product candidates, we have a clinical development candidate, MB07811, which we have recommended for clinical development for the treatment of high cholesterol and possibly obesity. Recommendation for clinical development refers to an internal process involving our analysis of relevant pre-clinical data and selection of compounds suitable for clinical development by us. MB07811 is designed to act by controlling the expression of certain genes in the liver that are important for making or using cholesterol as well as genes involved in the control of energy expenditure. We plan to file an Investigational New Drug application, or IND, for MB07811 and to commence clinical trials of MB07811 in 2006 if the preclinical data is supportive and the proposed clinical trials are cleared by the FDA.

We have expertise in liver diseases and in the pathways and proteins residing in the liver that significantly contribute to certain metabolic diseases or that are important for transporting drugs into the liver, acting upon them and expelling them from the body. These processes are referred to as drug uptake, metabolism and excretion, respectively. With this knowledge, we developed proprietary technologies, including two which we called NuMimetic and HepDirect, which we have used to develop our current product candidates and which we expect to use to expand our product pipeline in the future.

We use our NuMimetic technology to discover molecules that bind effectively and specifically to certain regulatory sites, called nucleotide binding sites, residing on proteins called enzymes that control the output of cellular pathways involved in metabolic diseases, or metabolic pathways. We have developed a library of these unique molecules, known as nucleotide mimetics, and have used this library to discover compounds that we believe will lower glucose, cholesterol or lipid levels. We used our NuMimetic technology to discover CS-917 and MB07803, and we are also using it in certain of our advanced research programs, in which we have identified lead drug compounds and shown them to have efficacy in animal models. In addition to our internal programs that use the NuMimetic technology, we are using this technology in a collaboration with Merck & Co., Inc. to discover new treatments for metabolic diseases such as type 2 diabetes (by a different mechanism than CS-917 and MB07803), hyperlipidemia and a disease associated with fatty livers, known as non-alcoholic steatohepatitis, by inhibiting cholesterol and lipid production in the liver by activating a protein kinase in the liver known as AMPK.

We use our HepDirect technology to target drugs selectively to the liver, resulting in increased levels of the active form of the drug in the liver and decreased levels in non-liver tissues. We believe this liver-targeting property may significantly improve drug efficacy and safety when compared to non liver-targeting therapies. Our HepDirect technology can potentially be used to improve certain currently marketed drugs or applied to certain drug candidates, resulting in new, proprietary drugs that may then be marketed by us or by companies we collaborate with that have compounds that would benefit from this approach. Pradefovir and MB07133 use our HepDirect technology, as do several of our advanced research programs. In addition to our internal programs that use the HepDirect technology, we have collaborated with Merck to discover new treatments for hepatitis C by applying our HepDirect technology and other liver-targeting technology to certain compounds supplied by Merck.

Our research programs focus 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. Our goal is to expand our clinical development pipeline by continuing to recommend additional new drug compounds for clinical development. We believe that a broad product pipeline will provide strong growth potential and reduce our reliance on the success of any single product candidate. We may also in-license technologies and products to complement our internal discovery efforts. We believe our advanced research programs have the potential to yield additional clinical development candidates. Once we recommend a drug compound for clinical development, the clinical development candidate undergoes pre-clinical development including scale-up, toxicology and formulations development. Successful compounds would then enter human clinical testing.

Our advanced research programs include:

a program that has used our HepDirect and other liver-targeting technology in a collaboration with Merck to identify drugs to treat hepatitis C infection. The funded research phase of this collaboration has ended. Merck is currently evaluating and/or may evaluate drug compounds discovered under the research phase of the collaboration to determine if one or more will be recommended for clinical development,

a program using our NuMimetic technology in a collaboration with Merck to treat metabolic diseases such as type 2 diabetes (by a different mechanism than CS-917 and MB07803), hyperlipidemia and a disease associated with fatty livers, known as non-alcoholic steatohepatitis, by inhibiting cholesterol and lipid production in the liver, and

a program using our HepDirect technology to treat liver fibrosis by inhibiting the overproduction of collagen in the liver.

Our goal is to be a leading biopharmaceutical company developing and commercializing novel drugs. We intend to accomplish this goal by executing our strategy of

advancing the development of our product candidates and developing a broad product pipeline,

continuing to enhance our expertise in liver pathways and metabolism and our related intellectual property rights,

pursuing a diversified development and commercialization strategy for our product candidates,

establishing additional partnerships based on HepDirect or our other proprietary liver-targeting technologies, and

becoming a fully-integrated pharmaceutical company.

Disease Backgrounds

Liver diseases such as hepatitis B, hepatitis C, primary liver cancer and liver cirrhosis represent some of the most widespread and serious diseases in the world. Metabolic diseases such as type 2 diabetes, hyperlipidemia, obesity and non-alcoholic steatohepatitis are major healthcare problems worldwide, but are especially prevalent in the U.S. and Europe. We believe that these metabolic diseases can be treated by targeting metabolic pathways that reside in the liver, such as the pathways responsible for the production of glucose, cholesterol and fat molecules. As a group, liver and metabolic diseases represent one of the largest pharmaceutical markets with worldwide sales of drugs targeting these diseases exceeding $30 billion annually.

Liver diseases are generally poorly treated with current drug therapies. Moreover, these marketed drugs generally show significant limitations, including poor tolerability, safety risks or inadequate efficacy in certain patients. Some existing anti-viral and anti-cancer drugs are not effective against diseases of the liver due to the liver s inability to effectively convert them to their active forms. The use of existing drugs for the treatment of liver diseases is further limited in some cases by dose-limiting toxicities which may occur when high levels of the drug accumulate in tissues outside the liver.

In contrast to liver diseases, many more drugs are available for treating metabolic diseases either alone or in combination with other drugs. However, while effective drug therapies exist for some patients, most are inadequately treated or controlled.

Over 60% of patients treated for type 2 diabetes remain above the targeted levels for glucose set by the American Diabetes Association. In addition, over 80% of patients with coronary heart disease, which is associated with hyperlipidemia, remain above the targeted levels for cholesterol set by the National Cholesterol Education Program. Obese patients or patients with non-alcoholic steatohepatitis are even more poorly treated with few drugs on the market showing suitable efficacy and safety for these patients. As a result, we believe more effective drugs are needed to treat these diseases.

Our Pipeline

The following table summarizes our product candidates currently in clinical development, our clinical development candidate and our advanced research programs in descending order from our most advanced product candidate, pradefovir:

(1) None of our product candidates have received regulatory approval in the U.S. or in foreign countries.

(2) Phase III clinical trials expected to commence in 2006.

(3) Phase I clinical trials expected to commence in 2006.

(4) We are collaborating with Merck to apply our HepDirect™ and other liver-targeting technologies to certain compounds for the treatment of hepatitis C infection.

Pradefovir: A HepDirect prodrug of adefovir for the treatment of hepatitis B

Pradefovir is an oral product candidate that has successfully completed Phase II clinical trials to evaluate its potential to treat hepatitis B, a serious liver infection. Although several marketed drugs target hepatitis B, the disease remains poorly treated. One currently marketed hepatitis B drug is Hepsera, a non-liver specific prodrug of the antiviral compound adefovir. 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. Hepsera offers advantages over existing drugs because it is not associated with a high incidence of viral resistance, but toxicity issues limit the doses at which it can be administered and therefore its efficacy in treating this disease. Pradefovir, on the other hand, is designed using our proprietary HepDirect technology to deliver high concentrations of adefovir to the liver, while limiting the amount of adefovir generated outside of the liver, thereby potentially significantly reducing dose-related toxicities. In pre-clinical studies, pradefovir has been shown to result in higher levels of the active form of Hepsera, adefovir, in the liver without significantly increased levels of adefovir in the bloodstream or kidney. In clinical studies conducted to date, pradefovir has reduced hepatitis B virus levels to a greater extent than Hepsera at doses that are associated with lower circulating adefovir levels. In these studies, pradefovir also appeared to be safe and well tolerated. We are developing pradefovir in partnership with Valeant, to whom we licensed worldwide commercialization rights. Pradefovir was formerly called remofovir and before that, Hepavir B.

Hepatitis B

Hepatitis B is a viral disease that causes inflammation of the liver. Hepatitis B is transmitted by contact with the blood or other body fluids of an infected person. Hepatitis B infection is often difficult to diagnose because, depending upon the severity of the infection, patients can either be asymptomatic or experience only general flu-like symptoms such as fatigue, nausea or vomiting. Without appropriate treatment, continued inflammation of the liver leads to progressive scarring, or fibrosis, and eventually may lead to liver cancer, resulting in death.

Hepatitis B is the most common serious liver infection in the world. Over two billion people worldwide, or approximately one-third of the world s population, have been infected at some time with hepatitis B, and approximately 400 million of those people are chronic carriers of the virus. Approximately 1.2 million deaths per year worldwide are hepatitis B related. The Centers for Disease Control and Prevention reports that, in the U.S., over 1.2 million people are chronically infected with hepatitis B and nearly 80,000 new infections occur every year.

Sales of anti-viral drugs for the treatment of hepatitis B in the seven largest pharmaceutical markets, which are comprised of the U.S., France, Germany, Italy, Japan, Spain and the U.K., are expected to nearly triple between 2000 and 2010. There is also an opportunity for substantial additional growth from potential sales of anti-viral drugs for hepatitis B in emerging markets including Eastern Europe and Asia. These regions have some of the highest rates of chronic hepatitis B infection in the world. There are currently over 300 million people with chronic hepatitis B infection in these emerging markets, representing greater than 75% of the total chronic infections worldwide.

Current Treatments

In the U.S., until recently, there were three approved treatments for chronic hepatitis B: Intron A, Epivir-HBV, also referred to as Zeffix (lamivudine) and Hepsera. Each of these therapies has limitations in the treatment of patients with Hepatitis B. For example, Intron A is effective only in a small fraction of hepatitis B patients and is generally poorly tolerated. Patients taking Epivir-HBV or Zeffix can develop significant resistance to lamivudine, the drug s active ingredient. We believe that induction of viral resistance is also a significant issue for certain hepatitis B product candidates that are currently in late stage clinical development. Hepsera, on the other hand, shows limited propensity to induce virus mutations that are resistant to drug therapy and has proven effective against lamivudine-resistant strains of hepatitis B. However, potential kidney toxicities limit the level at which Hepsera can be dosed. In March 2005, a fourth drug called Baraclude™ (entecavir) was approved. To date, Baraclude has not been shown to induce significant viral resistance in drug naïve patients. However, based on clinical data, lamivudine resistant patients respond less effectively to Baraclude therapy and exhibit a higher rate of viral resistance.

Hepsera, lamivudine and Baraclude all decrease virus levels, as measured by hepatitis B DNA in the blood serum. Nevertheless, further decreases are desirable since these reductions are not considered sufficient to cure the infection in the majority of patients. In 2003, the New England Journal of Medicine reported that a three-fold higher dose (30 mg) of Hepsera led to a more than ten-fold greater reduction in hepatitis B DNA in the blood serum of patients and consistent trends toward improvement in all measures of liver injury. However, this higher dose caused elevation in markers of kidney toxicity that prevented further development at that dose. As a result, we believe the approved dose of Hepsera (10 mg) may be suboptimal for the reduction of virus levels.

Pradefovir

Pradefovir and Hepsera are both prodrugs of 9, -[2 (Phosphonomethoxy) ethyl] adenine (PMEA), or adefovir. When the prodrug is converted to adefovir in patients with hepatitis B, it acts in the liver and leads to decreased viral levels. Pradefovir is a HepDirect prodrug that after oral administration is absorbed rapidly after which it is taken up by the liver and converted to the active form, adefovir. Hepsera, on the other hand, is converted to adefovir throughout the bloodstream. As a result of this difference in distribution, higher dosing of pradefovir is possible due to the reduced systemic and renal adefovir levels, providing potentially improved efficacy relative to Hepsera in the treatment of hepatitis B, based on results of a Phase II clinical trial, which is further discussed in the clinical trials section below.

Clinical Trials

Under our agreement with Valeant, Valeant is responsible for conducting and reporting the results of clinical studies of pradefovir, and is responsible for making all regulatory filings related to the product, including submission of INDs and other regulatory submissions to the FDA. The following information is based on information provided to us by Valeant in connection with our agreement, or otherwise announced by Valeant.

Valeant has completed two single-dose Phase I clinical trials of pradefovir in 47 healthy volunteers. Pradefovir was safe and well tolerated at all dose levels studied. These clinical trials evaluated the pharmacokinetic profile of pradefovir, indicating that pradefovir appeared to be converted to its desired form, adefovir, in humans.

Pradefovir was also studied in two 28-day, randomized, placebo-controlled, double-blind, dose-escalation Phase I clinical trials designed to evaluate safety and preliminary efficacy in 80 hepatitis B patients in the U.S. and Taiwan.

The hepatitis B patients in the 28-day U.S. Phase I clinical trial were divided into groups that received 5, 10, 30 or 60 milligrams of pradefovir or a placebo administered orally once a day. The patients in the 28-day Taiwanese Phase I clinical trial were divided into groups that received 5, 10, 20 or 30 milligrams of pradefovir or a placebo administered orally once a day. In each of the dose groups evaluated, pradefovir was safe and well tolerated, and patients treated with pradefovir exhibited a statistically significant reduction, as determined by a p-value of less than 0.05, in hepatitis B virus levels compared to patients treated with a placebo. The reduction in median hepatitis B virus levels, which was determined by measuring viral DNA, and the overall distribution of adefovir throughout the body were consistent with results expected for our HepDirect technology based on pre-clinical studies.

Based on these initial results, in July 2004 Valeant commenced a 12-month dose-ranging Phase II clinical trial of pradefovir the purpose of which was to select appropriate doses for Phase III clinical trials. This Phase II clinical trial was fully enrolled as of November 2004 and 24 week interim results which showed evidence of safety and efficacy were first reported by Valeant in July 2005 and presented at the American Association for the Study of Liver Diseases, or AASLD, meeting in November 2005. Initial results of the completed Phase II clinical trial were announced by Valeant and Metabasis in March 2006, and detailed results of the completed Phase II clinical trial will be presented at the 41st Annual Meeting of the European Association for the Study of the Liver in April 2006 in Vienna, Austria.

The Phase II clinical trial conducted by Valeant was an open-label, randomized, multiple dose clinical trial with 242 patients enrolled at 21 sites in the United States, Taiwan, Singapore and South Korea. Approximately half of the patients had been previously treated ineffectively with other drugs. Patients that have been previously treated ineffectively are considered to be more difficult to treat. The Phase II clinical trial consisted of five treatment groups: pradefovir 5, 10, 20 and 30 mg administered once a day (called QD administration), and Hepsera 10 mg (QD), with an overall treatment duration of 48 weeks.

The data from the Phase II clinical trial showed that the patient group that received 30 mg (QD) pradefovir achieved a 5.54 log (10) drop in hepatitis B viral (HBV) DNA, a measure of viral load, from baseline as compared to a 4.19 log (10) drop in the 10 mg (QD) Hepsera (adefovir dipivoxil) group ($p<0.001$). Pradefovir at doses of 10 and 20 mg (QD) also showed a statistically significant greater reduction in viral load compared to Hepsera. The following chart illustrates these results:

Pradefovir Phase 2 Week 48 Results (all patients)

Mean Log(10) HBV DNA Decline From Baseline

(Intent-to-Treat Analysis)

Baseline Mean HBV DNA	Week 48	p-Value Compared to

	Dose	Number of Patients	(Log (10) copies/mL)	Mean Decline in HBV DNA	Hepsera Control
Hepsera	10 mg QD	50	8.0	-4.19	N/A
Pradefovir	5 mg QD	47	7.9	-4.09	0.83
	10 mg QD	49	7.9	-4.84	0.007
	20 mg QD	48	8.0	-4.89	0.007
	30 mg QD	**48**	**8.2**	**-5.54**	**<0.001**

The percentage of patients in the 30 mg (QD) pradefovir cohort achieving undetectable HBV DNA (<400 c/mL) was almost double that of patients receiving 10 mg (QD) of Hepsera. The percentage of patients with HBV DNA of less than 400 c/mL were 45 percent, 63 percent, 56 percent, and 71 percent for the pradefovir 5, 10, 20, and 30 mg (QD) groups, respectively, and 36 percent for the Hepsera group.

No patient demonstrated an increase in serum creatinine levels over baseline of greater than or equal to 0.5 mg/dL. Serum creatinine levels are a marker for renal toxicity that has been associated with higher doses of adefovir. Renal safety was comparable between all treatment groups. There were no serious adverse events related to treatment. The most frequently reported adverse events were similar across all treatment groups, including Hepsera. No dose-related trends regarding safety were identified and no events resulted in a patient being withdrawn prematurely from treatment.

Valeant has reviewed results from the Phase II clinical trial with the FDA and intends to initiate Phase III clinical trials in 2006.

Pre-clinical Studies

Together with Valeant, we conducted pre-clinical studies of pradefovir in rats, mice and monkeys. These studies showed that animals treated with an oral dose of pradefovir exhibited higher levels of adefovir and its biologically active form, adefovir diphosphate, in the liver and lower levels of adefovir and adefovir diphosphate in tissues outside of the liver, including the kidney and gastrointestinal tract, relative to animals treated with a similar dose of Hepsera. Results from one of these studies are depicted in the chart below, which shows the profile of adefovir diphosphate levels, measured by nanomoles per gram, over a 24 hour period in the livers and kidneys of rats administered an oral dose of either pradefovir or Hepsera at a level of 30 milligrams per kilogram.

CS-917: A gluconeogenesis inhibitor for the treatment of type 2 diabetes

CS-917 is an oral product candidate for type 2 diabetes that we discovered using our proprietary NuMimetic technology. Data generated to date indicate that CS-917 inhibits a metabolic pathway in the liver called gluconeogenesis, which is responsible for the excessive production of glucose by patients with type 2 diabetes. We believe that CS-917 is the first product candidate to be studied in human clinical trials that is designed to directly block this pathway. In pre-clinical studies and two completed clinical trials, CS-917 has shown a statistically significant reduction in elevated blood glucose levels of the type that characterize type 2 diabetes. CS-917 is being developed in partnership with Daiichi Sankyo, and we retain co-promotion rights in North America.

Diabetes

There are two forms of diabetes: type 1 (insulin-dependent, juvenile-onset diabetes) and type 2 (adult-onset diabetes). Approximately 90% of diabetes patients have type 2 diabetes. Elevated blood glucose levels in type 2 diabetic patients result from decreased glucose metabolism combined with increased glucose production. Decreased glucose metabolism arises from a relative

underproduction of the hormone insulin by the pancreas, along with a decrease in the sensitivity of the body s tissues, such as muscle, liver and fat, to insulin action. Increased glucose production is caused by increased synthesis of glucose by the gluconeogenesis pathway in the liver. Over time, the chronically elevated blood glucose levels in type 2 diabetics can lead to many long-term complications such as coronary heart disease, stroke, blindness, peripheral vascular disease, kidney disease and nerve damage. Diabetes is a leading cause of death in the U.S.

Type 2 diabetes afflicts over 170 million people worldwide, with over 18 million afflicted in the U.S. Global sales of oral diabetes drugs currently exceed $10 billion annually, with the U.S. accounting for over 65% of the total sales.

Current Treatments

The United Kingdom Prospective Diabetes Study, a landmark 20-year clinical study completed in 1996, demonstrated that stringent control of blood glucose levels reduces the risk of the serious complications associated with type 2 diabetes. As a result of this study, the American Diabetes Association now recommends that levels of hemoglobin A1c be maintained under 7% in type 2 diabetic patients. However, at present no single marketed drug is capable of lowering hemoglobin A1c levels into the targeted range for a sustained period of time in the majority of patients with type 2 diabetes.

Drugs from each of the three major classes of oral diabetes drugs not only exhibit limited efficacy, but also are associated with less than desired tolerability and significant mechanism-based side effects. These drug classes include:

insulin secretion enhancers, which lower glucose levels by inducing insulin secretion from the pancreas. This drug class has been associated with a significant risk of hypoglycemia,

insulin sensitizers, which lower glucose levels by enhancing insulin sensitivity. This drug class has been associated with fluid retention, weight gain, and a risk of congestive heart failure, and

hepatic glucose output inhibitors, which lower glucose levels by inhibiting liver glucose production. The only drug in this class is metformin, which, based on a study reported in the medical journal Diabetes, inhibits glucose production by the liver by only approximately 20-25%, even when administered at doses higher than the commonly prescribed daily dose. Therefore, a more effective hepatic glucose output inhibitor may improve efficacy over metformin. Metformin therapy has been associated with an increased risk of lactic acidosis in certain patient populations, especially patients with kidney dysfunction. In addition, metformin therapy can lead to transient gastrointestinal disturbances such as nausea, diarrhea and vomiting, which can compromise patient compliance.

Certain widely used insulin secretion enhancers and insulin sensitizers, but not metformin, are also associated with increased weight gain. Since weight gain is known to exacerbate diabetes, physicians often prescribe metformin as a first line therapy to obese patients, who according to a recent study published in the medical journal Diabetes & Endocrinology comprise more than 90% of newly diagnosed type 2 diabetic patients.

In the United Kingdom Prospective Diabetes Study, obese patients treated with maximum doses of metformin or an insulin secretion enhancer showed a steady rise in hemoglobin A1c levels above the targeted range at three years. Progressively fewer patients were able to maintain baseline hemoglobin A1c levels at six years and nine years, respectively.

Once treatment with a single oral drug fails to adequately control glucose levels, diabetic patients typically are treated with one or more additional oral drugs. It is estimated that more than 75% of type 2 diabetic patients will require multiple oral drug therapies to attain adequate glucose control and just over 30% of type 2 diabetic patients will ultimately advance to a stage that requires daily insulin injections. We believe that because of the limitations in currently marketed drugs, the diabetes market is receptive to new drugs, and new therapeutic approaches have the potential to experience rapid clinical acceptance.

CS-917

Studies show that the elevated blood glucose levels that characterize type 2 diabetic patients are correlated with the overproduction of glucose by the liver, which arises from an increased rate of flow through the gluconeogenesis pathway. We believe that CS-917 is the first product candidate to be studied in human clinical trials that is designed to directly block the gluconeogenesis pathway by inhibiting an enzyme called fructose-1,6-bisphosphatase, or FBPase. We believe that FBPase represents an important control point within this pathway and a suitable target for inhibiting the overproduction of glucose found in type 2 diabetic patients. Pharmaceutical companies have tried to find inhibitors of FBPase, but to our knowledge have thus far

failed to discover compounds of sufficient potency and specificity to be considered as product candidates. Using our NuMimetic technology, we have identified molecules that effectively bind to the nucleotide-binding site on FBPase and potently and specifically inhibit FBPase activity in animal models.

We believe that CS-917 may be effective across a broad patient population because glucose overproduction by the liver is common to all type 2 diabetics regardless of disease stage or body mass. Unlike insulin sensitizers and certain insulin secretion enhancers, CS-917 does not cause weight gain in animals and is therefore expected to be appropriate for effective treatment of obese diabetics. Studies also show that CS-917 is effective in animal models of lean diabetes and that glucose lowering occurs independent of insulin levels. Taken together these characteristics may make CS-917 useful:

in advanced diabetics, a patient population commonly resistant to therapies dependent on insulin production such as insulin sensitizers and insulin secretion enhancers,

in early stage diabetes, and

in prediabetics where CS-917 may be effective in preventing or delaying the onset of diabetes.

Clinical Trials

To date, our partner Daiichi Sankyo has completed a number of Phase I clinical trials of CS-917 in healthy volunteers as well as Phase I and Phase II clinical trials of CS-917 in type 2 diabetic patients.

Results from two Phase II clinical trials provide evidence that CS-917 is capable of significantly lowering blood glucose levels in humans. The first Phase II clinical trial completed involved treatment of 39 type 2 diabetic subjects with CS-917 or a placebo once daily for 14 days using a randomized, placebo-controlled, double-blind clinical trial design. The patients were divided into groups that received 50, 100, 200 or 400 milligrams of CS-917 or a placebo. Patients were dosed in the morning following a ten hour overnight fast and then fasted an additional six hours. The efficacy endpoint of the clinical trial was a comparison of cumulative glucose levels over the six-hour fasting period following administration on day 14 relative to baseline levels (which are cumulative glucose levels determined for the same period prior to clinical trial initiation) in patients treated with CS-917, as compared to the change from baseline levels in patients treated with a placebo. CS-917 appeared to be safe and well tolerated and the primary efficacy endpoint of the clinical trial, demonstration of a statistically significant reduction in these cumulative glucose levels as determined by a p-value of less than 0.05 in patients treated with the highest dose of CS-917, was achieved. A p-value of less than or equal to 0.05 is generally considered to signify a statistically significant result, which means a result is unlikely to occur by chance. Furthermore, the reduction in glucose levels seen on day 14 compared to baseline levels was greater in all groups treated with CS-917 than that seen in the placebo-treated groups.

In the second Phase II clinical trial, 146 type 2 diabetic subjects were treated with CS-917 or a placebo administered two or three times per day for 28 days using a randomized, placebo-controlled, double-blind clinical trial design. The primary efficacy endpoint of the clinical trial was the change from baseline in the plasma glucose level measured after an overnight fast, often called the fasting plasma glucose level, on the morning

of day 29 following the last dose on the evening of day 28, as compared to the change measured in the patients that received a placebo over the same time period. In each case, the group of patients who received CS-917 showed a statistically significant reduction in fasting plasma glucose levels compared to the corresponding dose group that received a placebo, as determined by a p-value of less than 0.05.

The results of clinical trials to date indicate that CS-917 may need to be administered more than once daily, although this has not been definitively determined.

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. However, metformin, which reduces liver glucose production through an unknown mechanism, also raises lactate above normal levels in about 4% of patients with no apparent adverse clinical consequences. In the 14-day Phase II clinical trial of CS-917, two patients treated with the highest dose of CS-917 (400 milligrams) exhibited lactate levels above the normal range on each day they received CS-917. Lactate levels in both patients returned to normal levels prior to administration of the next scheduled dose. In the 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 clinical trial. However, one patient who received 200 milligrams of CS-917 twice a day was withdrawn from the clinical trial by the investigator on day 15 due to concerns over elevated lactate levels measured the previous day.

A larger and longer-term Phase II clinical trial designed to further evaluate the safety and effectiveness of CS-917 and to determine dosing levels for potential Phase III clinical trials was initiated in December 2004. In addition, a second clinical trial that involved administration of a relatively high dose of CS-917 to evaluate the timing of dose administration was also initiated at that time. Additional Phase I clinical trials evaluating concomitant administration of CS-917 with other drugs were also initiated, including a clinical trial evaluating the interaction of CS-917 with the marketed diabetes drug metformin.

In March 2005, we were notified by Daiichi Sankyo that two serious adverse events involving lactic acidosis had occurred in two patients in a Phase I clinical trial evaluating the interaction of CS-917 with metformin. The serious adverse events were resolved after medical intervention. After the adverse events occurred, the three clinical trials that were ongoing at that time were stopped by Daiichi Sankyo, while one Phase I 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 clinical trial 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. A high blood level of metformin is believed to cause mitochondrial toxicity which can cause lactic acidosis. These dangerous levels are known to occur in patients with significant renal dysfunction who are inappropriately given metformin. Consequently, metformin is contraindicated for use in patients with significant renal dysfunction.

The reason for the unexpectedly high blood levels of both drugs in these two patients is unknown at this time. In July 2005, after completing a comprehensive review of the program and the events and data surrounding the two serious adverse events, we and Daiichi Sankyo concluded that the lactic acidosis observed in the two patients was likely due to the significantly increased blood levels of metformin described above which in turn likely led to mitochondrial toxicity. Subsequently, Daiichi Sankyo decided that Phase IIb clinical trials of CS-917 as a mono-therapy could safely resume with precautions to assure that patients do not take CS-917 in combination with metformin.

In February 2006, based on reports from Daiichi Sankyo, after submission of the proposed clinical trial protocol to the FDA and approval by the institutional review board, or IRB, a Phase IIb clinical trial of CS-917 was initiated. This Phase IIb clinical trial will allow measurement of the regulatory endpoint, the blood level of hemoglobin A1c. Daiichi Sankyo has conducted and will likely conduct additional studies combining CS-917 with other diabetes drugs to assess both the safety and eventually the potential for enhanced efficacy with the combination. However, further combination of CS-917 and metformin will be avoided unless additional data suggests that the elevation of metformin blood levels as seen in the two patients can be avoided through patient exclusion or through the administration of CS-917 at lower doses or through other means. Should CS-917 eventually be approved and combination with metformin remains an issue, the FDA may require additional measures be taken during marketing, such as prominent warning labels known as black-box warnings, physician education programs and/or other steps regarding concomitant use of CS-917 and metformin.

Pre-clinical Studies

Results from clinical trials of CS-917 are consistent with the glucose-lowering effect observed in pre-clinical studies we conducted with Daiichi Sankyo in several animal models of diabetes. Studies in rats showed that daily oral administration of CS-917 lowered blood glucose when dosed chronically, or over an extended period of time. Moreover, maximum glucose lowering in these studies was better than or equal to the glucose lowering effects of insulin sensitizers and insulin secretion enhancers. CS-917 also lowered glucose in both obese and lean diabetes animal models. Like metformin, but unlike the insulin sensitizers and certain insulin secretion enhancers, CS-917 induced no weight gain in treated animals relative to untreated animals.

Pre-clinical studies indicated that the combination of maximally effective doses of an insulin sensitizer with an FBPase inhibitor may result in greater efficacy than either drug alone. The following chart shows the results of a study in which we administered to an animal model of obese diabetes either no drug, referred to as control, or maximally effective doses of the insulin sensitizer troglitazone, CS-917 or a combination of troglitazone and CS-917. Blood glucose levels were monitored over three weeks, measured as milligrams per deciliter of blood, and shown to decrease similarly between animals treated with troglitazone and CS-917. The drug combination, however, led to near normalization of blood glucose levels, which is approximately 150 milligrams per deciliter:

In addition to troglitazone, which is no longer marketed because of safety concerns, we have evaluated the combination of FBPase inhibitors with other currently marketed insulin sensitizers with similar results.

Pre-clinical studies in diabetes animal models support the use of CS-917 in advanced diabetic patients. As in humans, animal models with diabetes show increased glucose production as they age and their diabetes worsens. Our studies demonstrated that these animals respond poorly to insulin sensitizers and insulin secretion enhancers. In contrast, these animals respond well to CS-917, indicating glucose-lowering effects in both advanced stage and early stage animal models of the disease.

In addition, Daiichi Sankyo has shown that chronic dosing of CS-917 decreases the insulin dose required to maintain a target glucose level in a mouse model of diabetes. Based on these studies and other pre-clinical data, including glucose-lowering effects in non-human primates and oral bioavailability data and toxicology results from studies in both rats and non-human primates, Daiichi Sankyo moved CS-917 into clinical trials in July 2001.

MB07133: A HepDirect prodrug for the treatment of primary liver cancer

MB07133 is an intravenously administered product candidate in a Phase I/II clinical trial designed to evaluate safety and preliminary efficacy in a limited number of patients with primary liver cancer. Few treatment options exist, and no drug has been approved for treatment of primary liver cancer. MB07133 uses our HepDirect technology to target the active form of araC to the liver while decreasing levels of the active form of the drug in tissues outside of the liver. AraC is a marketed anti cancer drug used to treat leukemia. AraC s anti-cancer activity is associated with its ability to be converted to its biologically active form, araCTP. Treatment with araC does not result in the generation of efficacious levels of araCTP in the liver due to the failure of araC to be converted to an intermediate form called araCMP. Using our HepDirect technology we

designed MB07133 to deliver araCMP to the liver thereby providing a means to treat primary liver cancer. We retain all rights to MB07133.

Primary Liver Cancer

Primary liver cancer is a malignancy originating in the liver that often kills patients within six months after diagnosis with less than 10% of patients surviving for five years or more. Metastatic liver cancer, on the other hand, originates in other organs and then progresses to the liver. In the U.S., the American Cancer Society reports that primary liver cancer is the ninth leading cause of cancer mortality in men and is the twelfth leading cause of cancer mortality in women. The American Cancer Society estimates that approximately 18,500 new cases of primary liver cancer will be diagnosed in the U.S in 2006. Primary liver cancer is responsible for over 500,000 deaths per year worldwide.

While the definitive cause of primary liver cancer is unknown, it is well-recognized that patients with chronic liver diseases such as hepatitis B, hepatitis C, alcoholic cirrhosis and iron overload are at high risk for developing liver cancer over a

30-year period. In the U.S., Europe and Japan, hepatitis C is considered to be one of the leading risk factors associated with primary liver cancer. The incidence of primary liver cancer in these countries is expected to increase over the next 10 to 15 years due to the large number of people previously infected with hepatitis C whose disease has or will advance to liver cirrhosis. In the U.S. alone, the National Institutes of Health projects a four-fold increase over this period in patients with chronic hepatitis C.

We believe that given the current and projected primary liver cancer incidence levels, and the cost of similar cancer therapeutics, an approved drug for primary liver cancer could present a substantial worldwide commercial opportunity.

Current Treatments

Treatment methods for patients with primary liver cancer are typically determined by the stage of the disease at diagnosis. Patients are generally classified as eligible for surgical tumor resection, inoperable and non-terminal, or terminal. According to the American Cancer Society, on average, over a ten-year period, over 16% of patients have been treated by surgical tumor resection. Additionally, over 50% of patients are inoperable and non-terminal and 26% of patients are terminal. Patients who undergo successful tumor resection have a future life expectancy of about five years, whereas all other patients have an average life expectancy of less than one year. Treatment for inoperable and non-terminal patients is dependent on many factors. Liver transplantation represents the only method that can cure the disease, but few transplants are possible due to the severe shortage in liver donors and the high cost. Other alternatives involve 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. Other treatments include regional tumor destruction and chemotherapy. However, we believe the disease remains poorly treated, and there are no currently approved drug therapies for primary liver cancer.

MB07133

MB07133 uses our HepDirect technology to target the active form of araC to the liver while decreasing levels of the active form of the drug in tissues outside of the liver. AraC is a marketed anti cancer drug used to treat leukemia. AraC is effective against leukemia but not solid tumors, including primary liver cancer, in large part because the enzymes required for conversion of araC to araCTP exist predominantly in leukemic cells and bone marrow cells. Conversion of araC to araCTP in bone marrow results in the dose-limiting toxicity that is traditionally associated with araC therapy.

Using our HepDirect technology, we developed MB07133, a product candidate that produces higher levels of araCTP in the liver with little to no araCTP produced in the bone marrow. MB07133 causes higher levels of araCTP in the liver because it effectively bypasses the first step in the metabolic pathway used to convert araC to araCTP, which otherwise requires an enzyme that is present only at relatively low levels in the liver. At the same time, MB07133 produces low levels of araCTP in the bone marrow because it is not readily converted to araCTP in bone marrow and blood. We believe that this change in distribution of araCTP will maximize MB07133 s potential therapeutic effect on liver tumors while minimizing its toxicity.

Clinical Trials

In September 2003 we initiated a Phase I/II clinical trial designed to evaluate the safety and preliminary efficacy of MB07133 in non-terminal patients with inoperable primary liver cancer tumors in the U.S., Hong Kong and Taiwan. The clinical trial is an open label, dose escalation Phase I/II clinical trial in patients with confirmed primary liver cancer tumors involving continuous intravenous infusion of MB07133 for seven days followed by a 21-day recovery period. Patients may receive infusions until treatment failure up to a total of six infusions of MB07133. The goal of this clinical trial is to establish the maximum tolerated dose. In addition to safety, we are monitoring changes in tumor size, physical well-being and changes in blood chemistry. Once the maximum tolerated dose is identified, we plan to study MB07133 at that dose in a limited number of patients in order to evaluate its potential efficacy.

Pre-clinical Studies

MB07133 has been studied in animals and shown to produce a significantly different distribution of araC and araCTP when compared to animals treated with araC alone. In one study, rats treated with MB07133 demonstrated significantly higher levels of araCTP in the liver and significantly lower levels of araC and araCTP in the blood and bone marrow, respectively, than rats treated with only araC. The following charts show the results achieved in this study:

In another study, MB07133 and araC were continuously infused into rats for two days, after which the levels of araCTP in the liver and bone marrow were determined. The MB07133-treated rats showed high levels of araCTP in the liver, whereas araCTP was not detected in the livers of animals treated with araC alone. The opposite was observed in bone marrow, where araCTP levels were high in the rats treated with araC alone and not detected in the MB07133-treated rats. The level of araCTP achieved in the liver with MB07133 in these studies is above the levels of araCTP shown to kill human primary liver cancer cells in culture.

The differences in liver and bone marrow araCTP levels produced by MB07133 as compared to araC alone result in significant improvement in animal toxicology. Mice treated for five days with araC alone produced a dose-dependent decrease in body weight and a dose-dependent loss of bone marrow cells, whereas mice treated for the same period with MB07133 showed no loss in weight or bone marrow cells except at the highest dose, where a partial decrease in bone marrow cells was noted. We believe these results suggest that relative to araC, MB07133 may be able to deliver therapeutically active levels of araCTP to human primary liver cancer tumors with less toxicity.

MB07803: A second-generation gluconeogenesis inhibitor for the treatment of type 2 diabetes

Like CS-917, MB07803 is an oral product candidate for type 2 diabetes that we discovered using our proprietary NuMimetic technology. MB07803 is designed to have the same mechanism of action as CS-917 - it blocks the gluconeogenesis pathway in the liver by inhibiting FBPase. MB07803 is targeted to the same market and to have advantages over current therapies that are similar to those expected with CS-917. We retain all rights to MB07803.

In April 2002, upon completion of the discovery research portion of our collaboration with Daiichi Sankyo, we began work on a program designed to discover and develop second generation gluconeogenesis inhibitors. The goal of the second generation program was to discover and develop compounds with pharmaceutical properties that were improved over those seen to date with CS-917. One or more of these improvements, if they are demonstrated in subsequent clinical trials, may give second generation compounds certain advantages over CS-917. Should CS-917 prove to be an important new therapy for type 2 diabetes we believe the second generation could expand the use of this class further.

In October 2002, we entered into an exclusive option agreement with Daiichi Sankyo, under which Daiichi Sankyo paid us a non-refundable $8.5 million option fee that gave Daiichi Sankyo the right to negotiate a new agreement for the discovery,

development and licensing of second generation gluconeogenesis inhibitors, and an option to license an additional back-up compound discovered during the option period. In August 2003, Daiichi Sankyo exercised its right under the option agreement to designate an additional back-up compound and chose not to exercise its option to negotiate a new agreement for the discovery, development and licensing of second generation gluconeogenesis inhibitors, at which time the option expired. As a result, Daiichi Sankyo has no rights to compounds discovered under the second generation program and therefore we may develop these compounds on our own or in collaboration with another company.

In 2004, we recommended MB07803 for clinical development from this second generation program and in February 2006, we initiated a Phase I clinical trial of MB07803.

MB07811: A compound for the treatment of hyperlipidemia and possibly obesity

We currently have a clinical development candidate, MB07811, which we have recommended for clinical development for the potential treatment of high cholesterol and possibly obesity. MB07811 is the outgrowth of our efforts to find ways to control the expression of certain genes in the liver that are important for making or using cholesterol as well as genes involved in the control of energy expenditure. MB07811 is currently undergoing pre-clinical development including scale-up, toxicology (animal studies) and formulations development. It is anticipated that, if these efforts are successful, we would then enter MB07811 into human clinical testing.

Hyperlipidemia is a disease characterized by an elevation of lipids, such as cholesterol or triglycerides, in the bloodstream. Patients with hyperlipidemia have a greater risk of suffering heart attacks and other forms of heart disease. Global sales of cholesterol and triglyceride reducers used to treat hyperlipidemia currently exceed $20 billion, with over 60% of these sales occurring in North America. A person is generally considered obese under National Institutes of Health guidelines if he or she is 30 pounds or more overweight for his or her age, height, sex and bone structure. Approximately 60 million adults in the U.S. suffer from obesity. Obesity significantly raises the risk of illness or death from serious medical conditions including hypertension, type 2 diabetes, cardiovascular disease, stroke and certain cancers. In the U.S., obesity-related costs exceed $75 billion per year.

We have discovered a series of compounds that exhibit high liver specificity in animals and data indicate that these compounds can lower cholesterol in animals without causing toxicities associated with previously discovered compounds in the same class. The most advanced compound from this series, MB07811, was recommended for clinical development in 2005. Data generated in numerous preclinical models across six species indicate that MB07811 may be able to effectively lower serum cholesterol. Data from tests in a primate model indicate that MB07811 may lower serum cholesterol as effectively as the most widely prescribed statin, Lipitor® (atorvastatin) (see Chart A below) and is additive with Lipitor (see Chart B below).

Chart A

Chart B

We plan to file an IND for MB07811 and to commence clinical trials of MB07811 in 2006 if additional preclinical data is supportive and the proposed clinical trials are cleared by the FDA. We retain all rights to MB07811.

Our Research Programs

We are expanding our product pipeline by using our proprietary technologies, our knowledge of liver diseases, and our expertise in pathways and proteins residing in the liver that significantly contribute to metabolic diseases. We have additional expertise in processes in the liver that are important for drug uptake, metabolism and excretion, all of which are important for targeting drugs to the liver with high specificity. We have used this knowledge to develop our proprietary NuMimetic and HepDirect technologies, which we use in several of our research programs. We also have expertise in structure-based drug design and we have developed novel computational methods useful for predicting drug binding effectiveness and specificity. These methods have aided our design and discovery of novel nucleotide mimetics. Our goal is to expand our clinical development pipeline by continuing to recommend additional compounds for clinical development.

Our advanced research programs include:

A viral enzyme inhibitor for the treatment of hepatitis C

Hepatitis C is a viral disease that causes inflammation of the liver that may lead to cirrhosis, primary liver cancer and other long-term complications. Roughly 3% of the world population has been infected with hepatitis C. In the U.S., nearly 4 million people are infected with hepatitis C, of whom 2.7 million are chronically infected.

We have had a collaboration with Merck to create liver-targeting prodrugs of certain compounds that Merck is supplying to us. These compounds target the hepatitis C virus residing in the liver. The funded research phase of this collaboration has ended. Merck is currently evaluating the drug compounds discovered during the collaboration to determine if one or more will be recommended for clinical development. Merck is solely responsible for conducting and funding all development work for compounds resulting from this collaboration and for commercializing any resulting products.

A nucleotide mimetic targeting a protein kinase for the treatment of type 2 diabetes, hyperlipidemia and non-alcoholic steatohepatitis

Non-alcoholic steatohepatitis results from fatty liver disease, a condition associated with type 2 diabetes and obesity, and can ultimately lead to liver fibrosis and later cirrhosis. Based on the number of obese people in the U.S., it is projected that over 6.0 million people currently suffer from non-alcoholic steatohepatitis.

Using our NuMimetic technology, we have discovered a highly potent and selective nucleotide mimetic that activates a protein kinase found in the liver known as AMPK, which regulates cholesterol and fat levels. We have shown in animal models that our lead compound from this research program can inhibit cholesterol and fat synthesis. We believe that this compound or a related compound using our NuMimetic

technology may be useful for the treatment of metabolic diseases such as type 2 diabetes (by a different mechanism than CS-917 and MB07803), hyperlipidemia (by a different mechanism than MB07811), and a disease associated with fatty livers, known as non-alcoholic steatohepatitis, by inhibiting cholesterol and lipid production in the liver. We have entered into a second collaboration with Merck to research, develop and commercialize novel small molecule therapeutics that activate AMPK.

A liver-specific collagen inhibitor for the treatment of liver fibrosis

Liver fibrosis is a life-threatening disease characterized by excessive scarring of the liver, typically caused by chronic hepatitis B or hepatitis C infections or alcoholism, which in turn results in compromised liver function, or cirrhosis. It is estimated that at least 25,000 deaths are caused by chronic liver disease and liver cirrhosis each year in the U.S., almost half of which are attributable to alcoholism.

Liver fibrosis involves an overproduction in the liver of a protein called collagen. This overproduction leads to changes in liver structure and function, and ultimately to liver failure. Using our HepDirect technology, we have developed compounds that target an enzyme controlling collagen production in the liver and showed in animal models of liver disease that our approach led to reduced liver fibrosis.

We retain worldwide commercialization rights to all of the compounds generated from our advanced research programs with the exception of the compounds covered under our collaborations with Merck.

Our Proprietary Technologies

We have developed proprietary technologies that we have used to develop our current product candidates and which we expect to help us expand our product pipeline in the future. Our NuMimetic technology encompasses know-how and compound libraries that are useful in the discovery of molecules that bind effectively and specifically to nucleotide binding sites on certain key enzymes controlling important metabolic pathways. We used this technology to identify CS-917 and MB07803 and may continue to use it to help discover product candidates in other areas. Our HepDirect technology is a proprietary technology used to target drugs to the liver. We applied this technology to develop pradefovir and MB07133 and will continue to use it in programs focused on the discovery of drugs for liver diseases such as hepatitis C and liver fibrosis as well as metabolic diseases.

NuMimetic Technology

The liver plays a central role in many metabolic diseases. Metabolic pathways that reside in the liver are responsible for much of the body s generation of products such as cholesterol, glucose and lipids. This production is normally dependent on an individual s nutritional and hormonal status. However, in individuals with metabolic diseases, these pathways are improperly controlled, leading to excessive production of cholesterol, glucose and lipids.

We are studying enzymes found in the liver that directly or indirectly control the flux, or rate of flow, through these pathways. We believe that many of these enzymes use compounds called nucleotides as a signal for switching flow on or off. While nucleotides are more typically known as a cell s primary chemical energy form and its building blocks for DNA synthesis, they are also recognized as important regulators of metabolic pathways.

We believe that certain nucleotide-binding enzymes represent important drug targets. Nucleotides that bind to these enzymes affect enzymatic activity and therefore the flux through certain metabolic pathways. Certain enzymes important to glucose, cholesterol and fat production and metabolism are known to contain a nucleotide-binding site. It is likely that successful drug compounds targeting these sites will need to exhibit both high binding affinity and high enzyme specificity. Over the past two decades, efforts to find such compounds by screening large compound libraries have failed in large part due to the physical characteristics of these sites.

We have extensively studied the structure of certain nucleotide-binding sites to determine the structural elements that are important for binding and specificity. Through these efforts, we have discovered proprietary compounds that bind to these sites and simulate the action of the natural nucleotides. We have generated large libraries of these compounds, which are known as nucleotide mimetics. These libraries and the know-how generated from our studies constitute our NuMimetic technology.

The following diagram illustrates how our NuMimetic technology works:

HepDirect Technology

Developing drugs to treat diseases of the liver has been a major challenge for the pharmaceutical industry. Although companies have worked for decades to develop drugs that treat chronic liver diseases, relatively few drugs are commercially available. In addition, currently marketed drugs approved for chronic liver diseases generally show poor tolerability, have significant safety risks or are ineffective in the majority of patients. We believe a primary reason for these limitations is that many drugs cannot be delivered to the liver in sufficient quantities to be effective without leading to serious toxicity in other tissues.

Our HepDirect technology addresses these problems by delivering high concentrations of the biologically active forms of target drugs to the liver while simultaneously reducing drug exposure in other tissues. We accomplish this process by making a simple chemical modification that renders the target drug biologically inactive and more readily available to cells. We refer to the modified drug as a HepDirect prodrug. The following diagram illustrates how a HepDirect prodrug works:

Administration of HepDirect prodrugs results in their distribution throughout the body. HepDirect prodrugs, unlike most other prodrug classes, are generally stable in the blood and tissues outside the liver. Because of the limited capacity of non-liver tissues to metabolize and convert HepDirect prodrugs to their active forms, distribution into these tissues leads to rapid reappearance of the prodrugs into the blood stream and ultimately diffusion of the prodrugs from the blood into the liver. In the liver, HepDirect prodrugs are metabolized by an enzyme expressed predominantly in the liver (CYP3A4) which converts the prodrug to the biologically active form of the target drug. Because HepDirect prodrugs are metabolized primarily in the liver, higher target drug levels are achieved in the liver while target drug levels outside of the liver are diminished.

Our HepDirect technology is broadly applicable to a wide variety of drugs. In some cases, the technology may enable the use of drugs that are otherwise ineffective or poorly effective in a particular liver disease due to the drug s failure to achieve therapeutic levels in the liver or due to the inability to administer doses that achieve therapeutic levels as a consequence of drug-related toxicities outside of the liver.

We have shown that our HepDirect technology can deliver compounds with anti-viral, anti-cancer, or anti-fibrotic activity, and we are continuing to use this technology to discover innovative new products for treating liver diseases, and to deliver compounds that affect pathways in the liver responsible for metabolic diseases. For example, we are using this technology and other liver-targeting technologies in a collaboration with Merck in which we are creating prodrugs of certain compounds to target the hepatitis C virus residing in the liver. The funded research phase of this collaboration has ended. Merck is currently evaluating the drug compounds discovered under the research phase of the collaboration to determine if one or more will be recommended for clinical development.

Other Technologies

We have developed other proprietary technologies useful for discovering new candidates for treating diseases. These include additional proprietary methods for targeting the liver and structure-based drug design technologies. We continue to develop and refine our capabilities for identifying important new drugs.

Our Business Strategy

Our goal is to be a leading biopharmaceutical company developing and commercializing novel drugs. Important elements of our business strategy include:

Advancing the development of our product candidates. We currently have four product candidates in clinical trials, pradefovir for the treatment of hepatitis B, CS-917 and MB07803 for the treatment of type 2 diabetes and MB07133 for the treatment of primary liver cancer. We were responsible for the discovery and initial development of each of these product candidates. Valeant and Daiichi Sankyo are primarily responsible for further clinical development of pradefovir and CS-917, respectively. We participate on joint development teams, and we retain significant commercial interest in both product candidates, including North American co-promotion rights for CS-917. We are solely responsible for the development of, and have all rights to, both MB07803 and MB07133.

Continuing to develop a broad product pipeline. We are aggressively seeking to expand our pipeline of product candidates. Our goal is to expand our clinical development pipeline by continuing to recommend new drug compounds for clinical development. In 2005, we recommended the clinical development of MB07811, a clinical development candidate for the treatment of high cholesterol and possibly obesity. In addition, we have entered into a collaboration with Merck to create liver-targeting prodrugs of certain compounds that Merck is supplying to us. These compounds target the hepatitis C virus residing in the liver. We also have an advanced research program for the treatment of type 2 diabetes (by a different mechanism than CS-917 and MB07803) and the treatment of hyperlipidemia (by a different mechanism than MB07811) which is covered under our AMPK collaboration with Merck. These advanced research programs may yield additional drug compounds for clinical development. We retain worldwide commercialization rights to MB07811and all of the compounds generated from our advanced research programs, with the exception of compounds covered by our collaborations with Merck. Using our internal drug discovery capabilities and our HepDirect, NuMimetic and other proprietary technologies, we intend to discover and develop new drug compounds for the treatment of metabolic diseases, liver diseases and certain other diseases linked to pathways in the liver. In addition, at the appropriate time, and as resources allow, we may seek to expand our product pipeline 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.

Continuing to enhance our expertise in liver pathways and metabolism and related intellectual property rights. Our near-term strategy is to continue to develop proprietary drugs and technologies for the potential treatment of metabolic diseases, cancer and certain other diseases linked to pathways in the liver. We have extensive expertise in liver diseases, as well as pathways and proteins residing in the liver that significantly contribute to certain metabolic diseases or that are important for drug uptake, metabolism and excretion. We intend to continue to invest in our know-how and capabilities, including our HepDirect, NuMimetic and other technologies. Our expertise in this area gives us a competitive advantage for continuing to build a broad product pipeline. We will continue to pursue comprehensive intellectual property protection of our technologies and product candidates when appropriate.

Pursuing a diversified development and commercialization strategy for our product candidates. We have implemented a development and commercialization strategy that combines collaborative partnerships with our own internal product development and commercialization efforts. The revenues from license fees, milestone payments and research funding associated with these arrangements, combined with reduced clinical development expenses, will allow us to better manage our resources and focus on building new opportunities. At the same time, as appropriate, we retain rights that allow us to participate in the commercialization of our product candidates. This strategy is designed to develop and distribute our products as broadly and as effectively as possible while still allowing us to establish our own sales and marketing infrastructure as appropriate. For example, with CS-917, we have a strategic alliance whereby Daiichi Sankyo is responsible for conducting clinical trials, but we have retained an option to co-promote CS-917 in North America, while with MB07133 and MB07803, we are solely responsible for development of the product candidate and have retained all rights. Merck is responsible for conducting future clinical trials under our AMPK collaboration while we have retained the option to co-promote any resulting products in the United States. Our goal for future collaborations is to seek to establish them after we have demonstrated high value for the subject candidate, a strategy which we believe will allow us to retain greater control over development, participation and commercialization.

Establishing additional partnerships based on HepDirect or our other proprietary liver-targeting technologies. Our HepDirect and other proprietary technologies can help overcome some of the challenges faced in developing drugs for liver and metabolic diseases. We believe these technologies are broadly applicable to a wide variety of drug targets. We may partner these technologies with other biopharmaceutical companies whose products would benefit from improved liver-targeting. For example, in 2003 we entered into a collaboration with Merck to discover new treatments for hepatitis C. We created liver-targeted versions of certain compounds provided by Merck that target the hepatitis C virus residing in the liver. The funded research portion of this collaboration was recently completed. Merck is currently evaluating the drug compounds discovered under the research phase of the collaboration to determine if one or more will be recommended for clinical development.

Becoming a fully-integrated pharmaceutical company. We plan to become a fully-integrated pharmaceutical company. In time and as resources allow, we expect to rely less on collaborative arrangements with other

pharmaceutical companies and more on our own internal development, marketing and sales capabilities. We have relied and continue to rely on our partners for the development of our first two product candidates, pradefovir and CS-917. In contrast, we have managed the early clinical development of MB07133 and MB07803 entirely on our own. Still, we have not built an extensive and expensive infrastructure for this effort. Instead, we have relied on a network of consultants and contract research organizations to carry out this development program. We are expanding our internal infrastructure and intend to continue to do so over time as our pipeline expands and we further develop products internally.

Strategic Alliances

In some cases, we use strategic alliances and collaborative partnerships with pharmaceutical and biotechnology companies to augment our internal drug discovery and development capabilities, and to assist the commercialization of our products globally. The revenues from license fees, milestone payments and research funding associated with these arrangements, combined with clinical development expenses assumed by our partners, have allowed us to better manage our resources and focus on building new opportunities. We have generally structured our alliances and partnerships to license specific products, rather than technology, or to apply our technology to a partner s product, and we intend to continue this practice in the future.

Valeant

In October 2001, we entered into a development and license agreement with Valeant for the development and commercialization of pradefovir. Under the agreement, we granted Valeant exclusive worldwide rights to develop and commercialize pradefovir during the term of the agreement. We also agreed that, for so long as Valeant is continuing to develop or commercialize pradefovir, neither we nor our affiliates will develop or commercialize chemically similar compounds that use our HepDirect technology. We further agreed that if Valeant determines that further development of pradefovir is not desirable, Valeant will have the right to substitute one of these compounds, if available, for pradefovir (or the compound that is then under development by Valeant under our agreement). Valeant paid us a license fee of $2 million under the agreement and will be obligated to make milestone payments to us upon the occurrence of specified development, regulatory and commercial milestones. Valeant will pay royalties to us on sales, if any, of products licensed to Valeant under the agreement for the longer of (1) ten years from the first commercial sale or (2) the term of any valid patent right of pradefovir. If all development, regulatory and commercial milestones are achieved, and including the $2 million license fee, we may be entitled to payments which total up to $20 million, plus royalties. In addition, Valeant is solely responsible for conducting and funding all development work, although a joint development committee composed of representatives of Valeant and Metabasis is responsible for overseeing those development efforts. In the third quarter of 2002, Valeant initiated clinical testing of pradefovir for the treatment of hepatitis B. As of December 31, 2005, we had received $2 million in milestone payments under the agreement.

During the first five years of the agreement, if we decide to develop with a third party a compound using our HepDirect technology (other than the compound licensed to Valeant) for the treatment of hepatitis B in humans, Valeant will have a right of first participation to obtain rights in the compound. If Valeant exercises its right of first participation, we have agreed to negotiate in good faith during a limited negotiation period regarding the terms upon which we would grant Valeant those rights. These terms would include an upfront payment, research funding, development and regulatory milestone payments and royalty payments on sales of products, all of which are specified in the development and license agreement. If Valeant does not exercise its right of first participation or we are unable to negotiate the terms on which we would grant Valeant these rights, we may develop the compound with the third party. In addition, under the agreement, Valeant has a ten-year option to obtain an exclusive license to develop and commercialize any other HepDirect compound that we own or control that contains a certain anti-viral drug owned and controlled by Valeant and a five-year option to enter into additional collaborative arrangements with us relating to the application of our HepDirect technology to drug compounds for the treatment of hepatitis B that Valeant has a right to commercialize.

The term of the development and license agreement will continue until all of Valeant s royalty payment obligations have expired, unless the agreement is earlier terminated. The agreement may be terminated entirely or on a country by country basis by either party only for material breach of the other party which remains uncured.

Daiichi Sankyo

In April 1997, we established a multi-year research, development and commercialization collaboration with Daiichi Sankyo to discover, develop and commercialize FBPase inhibitors for the treatment of diabetes. The discovery research portion of the collaboration was extended in February 2000 and March 2001 and ended in April 2002. Under this agreement, our drug discovery efforts were fully funded by Daiichi Sankyo. Daiichi Sankyo had the right to select compounds discovered during the discovery period and is responsible for conducting and funding the clinical development of any compound selected for development. Daiichi Sankyo has exclusive, worldwide commercialization rights to products developed under the agreement. Daiichi Sankyo selected CS-917 as a clinical candidate in 1999 and initiated Phase I clinical trials of CS-917 in July 2001. A joint development committee composed of members from both Daiichi Sankyo and Metabasis oversees clinical development. Compounds that Daiichi Sankyo develops during the five-year period following completion of the drug discovery phase of the collaboration, which target type 1 or type 2 diabetes and act by direct suppression of hepatic gluconeogenesis by inhibiting FBPase, are also subject to the collaboration agreement.

As part of the collaboration, Daiichi Sankyo paid us license fees and sponsored research totaling $20.3 million over the five-year discovery research portion of the collaboration and made an investment of $7.3 million in our Series A preferred stock. As of December 31, 2005, Daiichi Sankyo had made three milestone payments totaling $6.5 million and is obligated to make additional payments based on the achievement of future clinical and regulatory milestones. If all clinical and regulatory milestones are achieved, and including the $20.3 million in license fees and sponsored research, the $7.3 million investment in our Series A preferred stock and the $8.5 million option fee referred to below, we may be entitled to payments which total up to $54.5 million. In addition, Daiichi Sankyo will pay us a royalty on net sales, in countries where we have not exercised our co-promotion rights, of any product developed under the collaboration

agreement for the longer of (1) ten years from the first commercial sale or (2) the term of any valid patent right of a product. In keeping with our partnering strategy, we have the option to co-promote CS-917 or any other product developed under the collaboration in North America on terms and conditions to be negotiated after we exercise the option. We have the contractual right to exercise our co-promotion option for CS-917 prior to the filing of a New Drug Application, or NDA, for CS-917.

In October 2002, we entered into an exclusive option agreement with Daiichi Sankyo, under which Daiichi Sankyo paid us a non-refundable $8.5 million option fee that gave Daiichi Sankyo the right to negotiate a new agreement for the discovery, development and licensing of second generation gluconeogenesis inhibitors, and an option to license an additional back-up compound discovered during the option period. In August 2003, Daiichi Sankyo exercised its rights under the option agreement to designate an additional back-up compound, which Daiichi Sankyo will have the option to license only in the event that the development of CS-917 and the current back-up compound are discontinued. Daiichi Sankyo has the right to terminate development of CS-917 and the current back-up compound and to substitute the additional back-up compound for CS-917 and the current back-up compound under the terms of our collaboration agreement. Also in August 2003, Daiichi Sankyo chose not to exercise its option to negotiate a new agreement for the discovery, development and licensing of second generation gluconeogenesis inhibitors, at which time the option expired. As a result, Daiichi Sankyo has no rights to MB07803, and we may therefore develop MB07803 on our own or in collaboration with another company. Because MB07803 may be directly competitive with CS-917 should they both be developed and because Daiichi Sankyo has no commercial or other rights to MB07803, the information that Metabasis receives from Daiichi Sankyo regarding CS-917 has been reduced.

The term of our collaboration agreement, including the license of the additional back-up compound under our option agreement, will continue until all of Daiichi Sankyo s royalty payment obligations have expired, unless the agreement is earlier terminated. The agreement may be terminated by either party only for material breach which remains uncured or for bankruptcy of the other party. In addition, on a country-by-country basis, we will be entitled to regain rights to CS-917 from Daiichi Sankyo if it does not diligently develop and market CS-917 in a particular country.

Merck

In December 2003, we entered into a collaboration agreement with Merck to discover new treatments for hepatitis C. Under this collaboration, we are creating liver-targeting prodrugs of certain compounds that Merck is supplying to us. These compounds target the hepatitis C virus residing in the liver. The research term of the collaboration was initially for one year and in January 2005, was extended for an additional year through December 2005. At the same time, the scope of the technology that we apply to the Merck compounds was expanded. As part of this collaboration, Merck paid us an upfront fee of $500,000 and research support totaling $2.7 million during 2004 and 2005. Merck is also obligated to pay pre-clinical and clinical milestone payments if specified development and regulatory events occur and royalties on sales of products resulting from the collaboration. If all pre-clinical and clinical milestones are achieved, and including the $500,000 upfront fee and the $1.4 million in research support for each of the first two research years, we may be entitled to payments which total up to $93.3 million, plus royalties. Merck is solely responsible for conducting and funding all development work for compounds resulting from the collaboration and for commercializing any resulting products.

During the initial one-year research term we agreed to work exclusively with Merck on research and development of compounds using our HepDirect technology for hepatitis C, except that our agreement with Merck allowed us to continue our internal hepatitis C research program during that time. Until the first anniversary of the date of our agreement, Merck had an option to extend this exclusivity period by paying us an exclusivity fee of $3.0 million. In January 2005, Merck informed us that it did not wish to exercise this option. The funded research phase of this collaboration has ended. Merck is currently evaluating the drug compounds discovered under the research phase of the collaboration to determine if one or more will be recommended for clinical development.

In addition, for a specified period following the effective date of the agreement, Merck has an exclusive option to obtain a license to develop and commercialize certain compounds from our internal program to discover antiviral compounds to treat hepatitis C. The parties have agreed upon the principal financial terms of any such license. If Merck exercises its option, the parties have agreed to negotiate in good faith during a limited negotiation period a separate written agreement that includes these financial terms, as well as other commercially reasonable terms to be negotiated by the parties. If Merck does not exercise its option to license a development candidate from our internal program before its expiration, or if, despite good faith negotiations, the parties do not enter into a separate written license agreement before the expiration of the negotiation period, then we retain all rights to that candidate including the right to license to another strategic partner.

The term of the collaboration agreement will continue until all of Merck s royalty payment obligations have expired, unless the agreement is earlier terminated. The agreement may be terminated by either party for material breach or insolvency of the other party. Merck also has the right to terminate the agreement without cause at any time after the end of the research term upon 90 days advance written notice to us.

In June 2005, we entered into a collaboration agreement with Merck to research, develop and commercialize novel small molecule therapeutics with the potential to treat several metabolic diseases including type 2 diabetes, hyperlipidemia and obesity by activating AMPK. As part of this collaboration, Merck paid an initial non-refundable license fee of $5.0 million in July 2005 and agreed to provide research support funding of a minimum of $2.1 million each year during the three-year research term. The three-year research term is subject to renewal for one additional year upon the parties mutual agreement. Our level of research activities, and the minimum research support funding, may be increased during the term upon mutual agreement of both parties. Merck is also obligated to pay milestone payments if specified preclinical and clinical development and regulatory events occur and to pay royalties on sales of any product resulting from this collaboration. We would also have the option to co-promote any such product in the United States. If all pre-clinical and clinical milestones are achieved on multiple indications, then including the $5.0 million initial, non-refundable license fee and the minimum $6.3 million in research support funding, we may be entitled to payments which total up to $74.3 million, plus royalties. Merck is solely responsible for conducting and funding all development work for compounds resulting from this collaboration.

The term of the collaboration agreement will continue until all of Merck s royalty payment obligations have expired, unless the agreement is earlier terminated. The agreement may be terminated by either party for material breach or insolvency of the other party. Merck also has the right to terminate the agreement without cause at any time after the end of the twenty-first month following the effective date upon 90 days advance written notice to us.

Sicor

As part of our June 1999 corporate restructuring, we agreed to pay Sicor Inc., now an indirect wholly-owned subsidiary of Teva Pharmaceutical Industries Ltd., a 2% royalty on our direct sales of products that would infringe one of our patents, patent applications, discoveries or inventions in existence as of our corporate restructuring, and 10% of any royalties we receive from licenses of these patents, patent applications, discoveries or inventions. We also agreed to pay Sicor a 1% royalty on our direct sales of products that use, contain or are based on our trade secrets, know-how and other proprietary rights in existence as of our corporate restructuring that are not covered by the 2% royalty, and 5% of any royalties we receive from licenses of these trade secrets, know-how and other proprietary rights that are not covered by the 10% royalty. Some or all of our current product candidates and drug compounds from our research programs may be subject to these royalty provisions.

Intellectual Property

Our success will depend in large part on our ability to:

obtain and maintain patent and other legal protections for the proprietary technology, inventions and improvements we consider important to our business,

prosecute and defend our patents,

preserve our trade secrets, and

operate without infringing the patents and proprietary rights of third parties.

We intend to continue to seek appropriate patent protection for our lead compounds, our proprietary technologies and their uses by filing patent applications in the U.S. and selected other countries. We intend for these patent applications to cover, where possible, claims for composition of matter, medical uses, processes for preparation and formulations.

As of February 1, 2006, we owned a total of 30 issued U.S. patents, 17 pending U.S. utility applications, and seven pending U.S. provisional applications. In foreign countries, as of the same date, we owned a total of 118 issued patents, five allowed applications and 171 pending applications.

Of the above applications and patents, we co-own one pending U.S. utility application, 18 foreign pending applications and one foreign allowed application with Daiichi Sankyo. We co-own one pending U.S. utility application, one pending U.S.

provisional application, and one foreign pending application with Merck. As of the same date, we held rights to a total of four in-licensed U.S. patents and 16 in-licensed foreign patents.

We believe we have a strong intellectual property position, including 13 issued U.S. patents, 23 pending U.S. applications, 76 foreign issued patents, five foreign allowed and 165 foreign pending applications that relate to proprietary technologies and compounds used in our current business. Our currently issued patents that relate to proprietary technologies and compounds used in our current business will expire between 2018 through 2021. The remaining currently issued patents that relate to our proprietary technologies and compounds that are no longer a primary focus of our current business will expire between 2006 and 2020.

Although we believe our rights under patents and patent applications provide a competitive advantage, the patent positions of pharmaceutical and biotechnology companies are highly uncertain and involve complex legal and factual questions. We may not be able to develop patentable products or processes, and may not be able to obtain patents from pending applications. Even if patent claims are allowed, 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 may be circumvented, challenged or invalidated by our competitors.

We also rely on trade secrets, proprietary know-how and continuing innovation to develop and maintain our competitive position, especially when we do not believe that patent protection is appropriate or can be obtained. Our policy is to require each of our employees, consultants and advisors to execute a proprietary information and inventions agreement before they begin providing services to us. Among other things, this agreement obligates the employee, consultant or advisor to refrain from disclosing any of our confidential information received during the course of providing services and, with some exceptions, to assign to us any inventions conceived or developed during the course of these services. We also require confidentiality agreements from third parties that receive our confidential information.

The biotechnology and biopharmaceutical industries are characterized by the existence of a large number of patents and frequent litigation based on allegations of patent infringement. As our current and potential product candidates and others based upon our proprietary technologies progress toward commercialization, the possibility of an infringement claim against us increases. While we attempt to be certain that our products and proprietary technologies do not infringe other parties patents and other proprietary rights, competitors or other parties may assert that we infringe on their proprietary rights.

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 related to these patents 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.

For a more detailed discussion of risks and uncertainties concerning intellectual property protection for our product candidates and proprietary technologies, see the section in Risk Factors entitled *Risks Related to Our Intellectual Property.*

Sales and Marketing

We do not currently have internal sales or marketing capabilities. In order to commercially market our product candidates if we obtain regulatory approval, we must either develop a sales and marketing infrastructure or collaborate with third parties with sales and marketing capabilities. We have granted Daiichi Sankyo and Valeant worldwide marketing and commercialization rights for CS-917 and pradefovir, respectively. However, we have retained a co-promotion option to directly market CS-917 in North America. In addition, at this point we have retained exclusive rights to MB07133, MB07803 and MB07811, as well as the compounds from our advanced research programs, with the exception of compounds that are covered by our collaborations with Merck.

We intend to make decisions regarding direct marketing of the product candidates for which we retain commercialization rights based on the data derived from our development and research programs in the future. If we proceed with direct marketing of any product candidates, we anticipate building a sales force designed to call on specialists that would be expected to prescribe the largest market share of the product candidate.

Competition

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, they may 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 diabetic patients, who are reported to comprise more than 90% of newly diagnosed type 2 subjects. In addition, inexpensive generic forms of metformin are available. Accordingly, unless CS-917 and/or MB07803 demonstrate a significant benefit over metformin or demonstrate that they can be used in the patient population who do not tolerate and/or adequately respond to metformin treatment, the price required to effectively compete with the generic form of metformin may be so low that it becomes uneconomical for us or Daiichi Sankyo to market CS-917 or for us to market MB07803.

Other currently marketed drugs that may compete with CS-917 and/or MB07803 include, but are not limited to the following classes:

sulfonylureas increase the secretion of insulin by the pancreas, thereby lowering the level of the sugar glucose in the blood,

insulins mimic the naturally occurring hormone insulin made by the pancreas to control blood glucose levels,

peroxisome proliferator-activated receptor agonists - improve insulin sensitivity by activating certain genes involved in fat synthesis and carbohydrate metabolism,

incretin mimetics mimic the naturally occurring hormone incretin . Incretin reduces blood glucose levels by increasing the secretion of insulin from the pancreas, slowing absorption of glucose from the gut, and reducing the action of glucagon (glucagon is a hormone that increases glucose production by the liver),

alpha-glucosidase inhibitors - decrease the absorption of carbohydrates from the intestine, resulting in a slower and lower rise in blood glucose throughout the day,

glinides - stimulate the pancreas beta-cells to produce insulin, and

metformin combination therapies combines metformin with members of the above-mentioned classes, particularly sulfonylureas and PPARs.

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

Currently approved treatments for hepatitis B in the U.S. that may compete with pradefovir are included in the following classes:

interferons - mimic the naturally occurring interferon . Interferon is an infection-fighting immune substance produced by the body,

nucleoside analogues - chemically engineered nucleoside compounds structurally similar to the building blocks of DNA and RNA that interferes with the replication of HBV, and

nucleotide analogues - chemically engineered nucleotide compounds structurally similar to the building blocks of DNA and RNA that interferes with the replication of HBV.

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

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

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

statins - reduce serum cholesterol levels by inhibiting a key enzyme involved in the biosynthesis of cholesterol,

fibrates reduce the amount of cholesterol and triglycerides (fatty substances) in blood,

nicotinic acid derivatives (NADs) - lower cholesterol and triglycerides. NADs decrease low density lipoproteins and increase high density lipoproteins,

cholesterol absorption inhibitors - inhibit the absorption of dietary and biliary cholesterol,

bile acid sequestrants bind with cholesterol-containing bile acids in the intestines and remove them in bowel movements, and

statin combination therapies - combine statins with members of the above-mentioned classes, particularly CAIs.

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

In addition, many other companies 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.

Manufacturing

Valeant and Daiichi Sankyo are responsible for all clinical and commercial manufacturing of pradefovir and CS-917, respectively. We rely on several suppliers to produce sufficient quantities of MB07133 and MB07803 for use in clinical studies and intend to rely on these or other suppliers to product sufficient quantities of MB07811 for use in future clinical studies. We currently intend to continue this practice for any future clinical trials and the possible large-scale commercialization of MB07133 and MB07803 and for any other potential products for which we retain significant development and commercialization rights. All of our current product candidates are small molecule drugs. These drugs are historically simpler and less expensive to

manufacture than biologic drugs. We believe our focus on small molecule drugs gives us a manufacturing advantage over companies that develop and manufacture biologic drugs.

Government Regulation and Product Approval

Our Product Candidates

Pradefovir, CS-917, MB07133, MB07803 and any other product candidates that we or our collaborators develop will require regulatory approval before they can be commercialized. Valeant and Daiichi Sankyo are responsible for clinical development and regulatory approval of pradefovir and CS-917, respectively, although we jointly oversee the clinical development of these product candidates through our participation in joint development committees. Although our collaborations with Merck have not yet yielded a product candidate, should either of them be successful, we will be dependent on Merck for clinical development and regulatory approval of any resulting product candidate. We are solely responsible for clinical development and regulatory approval of MB07133 and MB07803.

Product Regulation

Governmental authorities in the U.S. and foreign countries regulate, among other things, the pre-clinical and clinical testing, manufacturing, labeling, storage, record-keeping, advertising, promotion, export, marketing and distribution of drug products. In the U.S., pharmaceutical products are regulated by the FDA under the Federal Food, Drug, and Cosmetic Act, its implementing regulations and other federal laws and regulations. Both before and after the FDA approves a product, the manufacturer and the holder of the product approval are subject to comprehensive regulatory oversight. Violations of regulatory requirements at any stage, including the pre-clinical and clinical testing process, the NDA approval process, or the post-FDA-approval marketing of the product, may result in various adverse consequences. These adverse consequences may include a clinical hold on an ongoing study, the FDA s delay in approving or refusal to approve a product, suspension of manufacturing or withdrawal of an approved product from the market, seizure or recall of a product or the imposition of criminal or civil penalties against the manufacturer or the holder of the product approval. In addition, later discovery of previously unknown problems may result in restrictions on a product, its manufacturer, or the NDA holder, or market restrictions through labeling changes or product withdrawal. Also, new government requirements may be established that could delay or prevent regulatory approval of our products under development.

The steps required before a new drug may be approved for marketing in the U.S. generally include:

conducting appropriate pre-clinical laboratory tests and pre-clinical studies in animals in compliance with the FDA s Good Laboratory Practice, or GLP, requirements,

the submission of the results of these evaluations and studies to the FDA, along with manufacturing information and analytical data, in an IND for human clinical testing, which must become effective before human clinical trials may commence,

obtaining approval of institutional review boards, or IRBs, to introduce the product into humans in clinical studies,

conducting adequate and well-controlled human clinical trials to establish the safety and efficacy of the product, in compliance with FDA s Good Clinical Practice, or GCP requirements,

the submission of the results of pre-clinical studies, clinical studies, and adequate data on chemistry, manufacturing and control information to the FDA in an NDA, and

FDA review and approval of the NDA, including potential pre-approval inspections of manufacturing and testing facilities to assess compliance with the FDA s current Good Manufacturing Practice, or CGMP, requirements and other FDA regulations.

Pre-clinical studies generally include animal studies to evaluate the product s mechanism of action, safety and efficacy. Compounds must be produced according to applicable CGMP requirements, and pre-clinical safety tests must be conducted in compliance with FDA s GLP and similar international regulations. The results of the pre-clinical tests, together with manufacturing information and analytical data, are generally submitted to the FDA as part of an IND, which must become

effective before human clinical trials may be commenced. The IND automatically becomes effective 30 days after receipt by the FDA, unless the FDA before that time requests an extension or raises concerns about the conduct of the clinical trials described in the application. The sponsor of the application and the FDA must resolve any outstanding concerns before clinical trials can proceed. Clinical trials involve the administration of the investigational product to healthy volunteers or to patients with the disease or disorder being tested, under the supervision of a qualified principal investigator, and must be conducted in accordance with good clinical practices and other requirements, including the informed consent of human test subjects. Clinical trials are conducted in accordance with protocols that detail many items, including:

the objectives of the study,

the parameters to be used to monitor safety, and

the efficacy criteria to be evaluated.

Each protocol must be submitted to the FDA as part of the IND. Further, each clinical study must be reviewed and approved by an IRB at each institution at which the study will be commenced, prior to the recruitment of subjects. The IRB will consider, among other things, ethical factors, the safety of human subjects and the possible liability of the institution.

Clinical trials typically are conducted in three sequential phases, but the phases may overlap. In Phase I, the initial introduction of the drug into human subjects, the drug is tested in healthy volunteers or, on occasion, in patients, for safety and, as appropriate, for absorption, metabolism, distribution, excretion, pharmacodynamics, pharmacokinetics and other preliminary measures of efficacy. Phase II usually involves initial studies designed to identify doses of the drug that result in suitable efficacy, safety and tolerance in patients with the targeted disease. A clinical trial designed to generate efficacy data but that is not expected to satisfy FDA criteria for NDA approval is sometimes referred to as a Phase IIb study. Phase III clinical trials, commonly referred to as pivotal studies, are undertaken to provide proof of clinical efficacy and to provide sufficient evidence of safety to justify FDA approval, typically within an expanded and diverse patient population at multiple, geographically dispersed clinical study sites. Phase I, Phase II or Phase III testing may not show sufficient safety or efficacy within any specific time period, if at all, with respect to any products being tested. Furthermore, the sponsor, the FDA or the IRB may suspend clinical trials at any time on various grounds, including a finding that the healthy volunteers or patients are being exposed to an unacceptable health risk.

The results of the pre-clinical studies and clinical trials, together with detailed information on the manufacture and composition of the product, are submitted to the FDA as part of an NDA requesting approval for the marketing of the product. The cost of preparing and submitting an NDA is substantial.

The FDA has 60 days from its receipt of an NDA to determine whether the application will be accepted for filing based on the agency s threshold determination that the NDA is sufficiently complete to permit substantive review. Once the submission is accepted for filing, the FDA begins an in-depth review of the NDA. Under federal law, the FDA has agreed to certain performance goals in the review of NDAs. The goal for review of most such applications for non-priority drug products is ten months and for priority drug products is six months. The review process is often significantly extended by FDA requests for additional information or clarification regarding information already provided in the submission. The FDA may also refer applications for novel drug products or drug products which present difficult questions of safety or efficacy to an advisory committee, typically a panel that includes clinicians and other experts, for review, evaluation and a recommendation as to whether the application should be approved. The FDA is not bound by the recommendation of an advisory committee.

If FDA evaluations of the NDA and the manufacturing facilities are favorable, the FDA may issue an approval letter, or, in some cases, an approvable letter followed by an approval letter. An approvable letter generally contains a statement of specific conditions that must be met in order to secure final approval of the NDA. If and when those conditions have been met to the FDA s satisfaction, the FDA will typically issue an approval letter. An approval letter authorizes commercial marketing of the drug with specific prescribing information for specific indications. As a condition of NDA approval, the FDA may require post approval testing and surveillance to monitor the drug s safety or efficacy and may impose other conditions, including labeling restrictions which can materially impact the potential market and profitability of the drug. Once granted, product approvals may be withdrawn if compliance with regulatory standards is not maintained or problems are identified following initial marketing.

Once the NDA is approved, a product will be subject to certain post-approval requirements, including requirements for adverse event reporting and submission of periodic reports. Additionally, the FDA also strictly regulates the promotional

claims that may be made about prescription drug products. In particular, the FDA requires substantiation of any claims of superiority of one product over another including, in many cases, requirements that such claims be proven by adequate and well controlled head-to-head clinical trials. To the extent that market acceptance of our products may depend on their superiority over existing therapies, any restriction on our ability to advertise or otherwise promote claims of superiority, or requirements to conduct additional expensive clinical trials to provide proof of such claims, could negatively effect the sales of our products and/or our costs.

If the FDA s evaluation of the NDA submission or manufacturing facilities is not favorable, the FDA may refuse to approve the NDA or issue a not approvable letter.

The not approvable letter outlines the deficiencies in the submission and often requires additional testing or information in order for the FDA to reconsider the application. Even with submission of this additional information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval. With limited exceptions, FDA may withhold approval of an NDA regardless of prior advice it may have provided or commitments it may have made to the sponsor.

FDA approval of any application may entail many delays or never be granted. Moreover, if regulatory approval of a product is granted, the approval may include limitations on the uses or patient populations for which the product may be marketed. Further, product approvals may be withdrawn if compliance with regulatory standards is not maintained or if safety or manufacturing problems occur following initial marketing. Finally, if there are any modifications to the drug, including changes in indications, labeling or manufacturing processes or facilities, we or our collaborators may be required to submit and obtain FDA approval of a new NDA or NDA supplement, which may require the development of additional data or the conduct of additional pre-clinical studies and clinical trials.

Among the conditions for approval is the requirement that the prospective manufacturer s quality control, recordkeeping and manufacturing procedures conform to CGMP requirements enforced by the FDA through its facilities inspection program. In addition, product manufacturing facilities in California are subject to licensing requirements of the California Department of Health Services. These requirements must be followed at all times in the manufacture of the approved product, and manufacturing facilities are subject to inspection by the FDA and the California Department of Health, or other applicable governmental authorities, at any time. In complying with these requirements, manufacturers must continue to expend time, money and effort in the area of production and quality control to be certain of full compliance. The applicable requirements are complex, can be subject to differing interpretations and are subject to change without clear advance notice or guidance from the FDA. Any failure to comply with these requirements may subject manufacturers to, among other things, notices or letters detailing alleged deviations and demanding corrective actions, actions seeking fines and civil penalties, suspension or delay in product approvals, product seizure or recall, suspension of manufacturing, or withdrawal of product approval.

Once an NDA is approved, the product covered thereby becomes a listed drug which can, in turn, be cited by potential competitors in support of approval of an abbreviated NDA, or ANDA. An ANDA provides for marketing of a drug product that has the same active ingredients in the same strengths and dosage form as the listed drug and has been shown through bioequivalence testing to be therapeutically equivalent to the listed drug. There is no requirement, other than the requirement for bioequivalence testing, for an ANDA applicant to conduct or submit results of pre-clinical or clinical tests to prove the safety or effectiveness of its drug product. Drugs approved in this way are commonly referred to as generic equivalents to the listed drug, are listed as such by the FDA, and can often be substituted by pharmacists under prescriptions written for the original listed drug.

There are limitations on the timing of FDA s ability to approve an ANDA for a generic equivalent of a listed drug. In the event that the sponsor of the listed drug has properly informed FDA of patents covering its listed drug, applicants submitting an ANDA referencing that drug are required to certify whether they intend to market their generic products prior to expiration of those patents. If an ANDA applicant certifies that it believes one or more listed patents are invalid or not infringed, it is required to provide notice of its filing to the NDA sponsor and the patent

holder. If the patent holder then initiates a suit for patent infringement against the abbreviated NDA sponsor within 45 days of receipt of the notice, FDA cannot grant effective approval of the ANDA until either 30 months has passed or there has been a court decision holding that the patents in question are invalid or not infringed. A holding that a valid and enforceable listed patent is infringed will preclude approval of the ANDA until the expiration of that patent. If the ANDA applicant certifies that it does not intend to market its generic product before some or all listed patents on the listed drug expire, then FDA cannot grant effective approval of the ANDA until those patents expire. Under Federal law, the term of a patent covering a new chemical entity can be extended by up to five years, for an effective patent life of up to 14 years after approval, based on restoration of part of the patent life lost during clinical testing and FDA review.

Federal law also provides for periods of non-patent exclusivity that also limit the timing of potential approval of an ANDA for a generic equivalent to a listed drug. These include a period of three years of non-patent exclusivity following approval of a listed drug that contains previously approved active ingredients but is approved in a new dosage, dosage form, route of administration or combination, or for a new use, the approval of which was required to be supported by new clinical trials conducted by or for the sponsor, during which such three year period FDA cannot grant effective approval of an ANDA based on that listed drug. Federal law also provides a period of five years following approval of a drug containing no previously approved active ingredients, during which an ANDA for a generic equivalent cannot be submitted unless the submission accompanies a challenge to a listed patent, in which case the submission may be made four years following the original product approval.

The first abbreviated new drug applicant submitting a substantially complete application certifying that listed patents for a particular product are invalid or not infringed may qualify for a period of 180 days after a court decision of invalidity or non-infringement or after it begins marketing its product, whichever occurs first, during which subsequently submitted abbreviated NDAs cannot be granted effective approval. Similar non-patent exclusivity restrictions and patent certification requirements apply to so-called 505(b)(2) NDA applications which rely, in part or in whole, on data generated by or for parties other than the applicant to support an NDA approval.

FDA also imposes a number of complex requirements and restrictions on entities that advertise and promote prescription drugs, which include, among others, standards for and regulations of print and in-person promotion, product sampling, direct-to-consumer advertising, off-label promotion, industry sponsored scientific and educational activities, and promotional activities involving the Internet. The FDA has very broad enforcement authority under the Federal Food, Drug and Cosmetic Act, and failure to abide by FDA requirements can result in penalties and other enforcement actions, including the issuance of warning letters or other letters objecting to violations and directing that deviations from FDA standards be corrected, total or partial suspension of production, and state and federal civil and criminal investigations and prosecutions.

Federal regulations and FDA policies prohibit a sponsor or investigator, or any person acting on behalf of a sponsor or investigator, from representing in a promotional context that an investigational new drug is safe or effective for the purposes for which it is under investigation. Prior to approval of a product candidate, any assertion that one of our product candidates is safe or effective for any purpose or that it is superior to any currently approved product could result in regulatory action by FDA and could delay approval of the product candidate.

A variety of Federal and state laws apply to the sale, marketing and promotion of pharmaceuticals that are paid for, directly or indirectly, by Federal or state health care programs, such as Medicare and Medicaid. The restrictions imposed by these laws are in addition to those imposed by the FDA and corresponding state agencies. Some of these laws significantly restrict or prohibit certain types of sales, marketing and promotional activities by pharmaceutical manufacturers. Violation of these laws can result in significant criminal, civil, and administrative penalties, including imprisonment of individuals, fines and penalties and exclusion or debarment from Federal and state health care and other programs. Many private health insurance companies also prohibit payment to entities that have been sanctioned, excluded, or debarred by Federal agencies. We are also subject to various laws and regulations regarding laboratory practices, the experimental use of animals, and the use and disposal of hazardous or potentially hazardous substances in connection with our research. In each of these areas, as above, the FDA and other agencies have broad regulatory and enforcement powers, including the ability to impose fines and civil penalties, suspend or delay issuance of approvals, seize or recall products, and withdraw approvals, any one or more of which could have a material adverse effect upon us.

Other Regulations

We are also subject to regulation by the Occupational Health and Safety Administration and state and federal environmental protection agencies, and to regulation under the Toxic Substances Control Act. We may in the future be subject to additional federal, state or local regulations. The Occupational Health and Safety Administration or these environmental protection agencies may promulgate regulations that may affect our research and development programs. We cannot predict whether any agency will adopt any regulation which could limit or impede our operations.

Environmental and Safety Matters

We use hazardous chemicals, biological agents and various radioactive isotopes and compounds in our research and development activities. Accordingly, we are subject to regulations under federal, state and local laws regarding employee safety, environmental protection and hazardous substance control, and to other present and possible future federal, state and local regulations. We may also incur significant costs

complying with environmental laws and regulations adopted in the future.

Also, although we believe our current safety procedures for handling and disposing of hazardous 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. In the event of contamination or injury, we could be held liable for damages or penalized with fines in an amount exceeding our resources, and our clinical trials or regulatory approvals could be suspended.

Employees

As of December 31, 2005, we employed 95 full-time employees, consisting of 72 employees in research, development and regulatory affairs and 23 in management, administration, finance, receiving and facilities. As of the same date, 35 of our employees had a Ph.D. or M.D. degree. None of our employees is subject to a collective bargaining agreement. We consider our relationship with our employees to be good.

Scientific Advisory Board

We have established a scientific advisory board consisting of medical professors and industry experts with knowledge of our target markets. Our scientific advisors generally meet once a year as a group to assist us in formulating our research, development and clinical strategies. Some individual scientific advisors consult with and meet informally with us on a more frequent basis. We have entered into consulting agreements with all of our scientific advisors, but they 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.

Corporate Information

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.

Available Information

We make available free of charge on or through our Internet website our annual report on Form 10-K, quarterly reports on Form 10-Q, current reports on Form 8-K, and amendments to those reports, as soon as practicable after we electronically file these materials with, or furnish them to, the Securities and Exchange Commission. The address of our website is http:/ /www.mbasis.com. The information contained in, or that can be accessed through, our website is not part of this annual report on Form 10-K.

Item 1A. Risk Factors

You should consider carefully the following information about the risks described below, together with the other information contained in this annual report on Form 10-K and in our other filings with the Securities and Exchange Commission, before you decide to buy or maintain an investment in our common stock. We believe the risks described below are the risks that are material to us as of the date of this annual report. 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 candidate, 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 four current product candidates, pradefovir, CS-917, MB07133 and MB07803, and our current clinical development candidate, MB07811. Clinical trials conducted to date in patients treated with pradefovir have provided evidence of efficacy as measured by various parameters that we believe to be clinically and statistically significant. However, no pivotal, adequate and well-controlled clinical investigations designed to provide clinical and statistically adequate proof of efficacy, or to provide sufficient evidence of safety to justify approval, have been completed with any of our products. All of our product candidates will require

additional development, clinical trials and regulatory clearances before they can be commercialized. Positive results from pre-clinical studies and early clinical trials do not necessarily mean later clinical trials will succeed. Our product development efforts may not lead to commercial drugs, either because our product candidates 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 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 or clinical development candidate 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 and/or our partners, as applicable, may be unable to commercialize them successfully for a variety of reasons. These include, for example, the availability of alternative treatments, lack of cost effectiveness, the cost of manufacturing the product on a commercial scale and the effect of competition with other drugs. The success of our product candidates 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 and our commercialization collaborators, as applicable, will be unable to commercialize these products.

To receive regulatory approval for the commercialization of pradefovir, CS-917, MB07133, MB07803 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 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:

clinical trials may produce negative or inconclusive results,

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

costs of clinical trials may be greater than we anticipate,

our product candidates may cause undesirable side effects that delay or preclude regulatory approval or limit their commercial use or market acceptance if approved,

collaborators who are responsible for clinical trials of our product candidates may not devote sufficient resources to these clinical trials or conduct them in a timely manner, or

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

Success in 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 our product candidates have been tested in less than the number of patients that will likely need to be studied to gain regulatory approval. The data collected from clinical trials with larger patient populations may not demonstrate sufficient safety and efficacy to support regulatory approval of these product candidates.

The targeted endpoints for clinical trials of pradefovir and CS-917 have been, and will continue to be, primarily established by Valeant and Daiichi Sankyo, respectively. We are solely responsible for establishing the targeted endpoints for clinical trials of MB07133 and MB07803, as well as MB07811 should we initiate clinical trials of that clinical development candidate, as we currently expect. 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, could lead to lactic acidosis, a serious and potentially fatal condition. Certain pre-clinical animal studies have shown that CS-917 raises lactate levels two- to three-fold in some but not all animal models. Elevated lactate levels have also been observed in certain human clinical trials of CS-917. For example, in a 28-day Phase 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 clinical trial. However, one patient who received 200 milligrams of CS-917 twice a day was withdrawn from the clinical trial by the investigator on day 15 due to concerns over consistently elevated lactate levels measured the previous day. Other incidences of elevated lactate levels have been observed and will likely occur in the future.

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

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

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

It is also possible that CS-917 and MB07803 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 pradefovir 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 may have other significant adverse implications on our business, for example:

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

our stock price could decline,

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

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

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

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

we may be unable to attract and retain key employees.

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

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

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

our reputation may suffer.

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

We are dependent on our collaborations with Valeant and Daiichi Sankyo for development of pradefovir and CS-917, 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 Valeant and Daiichi Sankyo for the development and commercialization of pradefovir and CS-917, respectively. Valeant and Daiichi Sankyo have agreed to finance the clinical trials for pradefovir and CS-917, respectively, and, if they are approved, manufacture and market them. Accordingly, we are dependent on Valeant and Daiichi Sankyo to gain FDA and other foreign regulatory agency approval of, and to commercialize, pradefovir and CS-917. We have also entered into two collaborations with Merck. 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 a candidate ultimately be selected, 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, MB07803 and MB07811 we may need to enter into additional collaborative agreements to assist in the development and commercialization of some of these potential products. However, our discussions with potential collaborators may not lead to the establishment of new collaborations on acceptable terms, if at all, or it may take longer than expected to establish new collaborations, leading to development and commercialization delays.

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

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

we do not achieve our objectives under our collaboration agreements,

we are unable to obtain patent protection for the product candidates or proprietary technologies we discover in our collaborations,

we are unable to manage multiple simultaneous product discovery and development collaborations,

our potential collaborators are less willing to expend their resources on our programs due to their focus on other programs or as a result of general market conditions,

our collaborators become competitors of ours or enter into agreements with our competitors,

we or our collaborators encounter regulatory hurdles that prevent commercialization of our product candidates,

we develop products and processes or enter into additional collaborations that conflict with the business objectives of our other collaborators,

consolidation in our target markets limits the number of potential collaborators, or

we are unable to negotiate additional collaboration agreements under terms satisfactory to us.

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

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

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

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

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

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

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

uncertainty regarding ownership of intellectual property rights arising from our collaborative activities, which could prevent us from entering into additional collaborations, or disagreements with our collaborators regarding the protection of intellectual property rights,

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

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

candidates.

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

We intend to use our proprietary technologies and our knowledge and expertise to develop and commercialize **novel drugs to address some of the world s most widespread and costly chronic diseases** involving pathways in the liver. Our goal is to expand our clinical development pipeline by continuing to recommend new drug compounds for clinical development. However, the process of researching and discovering drug compounds is expensive, time-consuming and unpredictable. Data from our current research programs may not support the clinical development of our lead compounds or other compounds from these programs, and we may not identify any additional drug compound suitable for recommendation for clinical development. Moreover, any drug compounds we recommend for clinical development may not demonstrate, through pre-clinical 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.