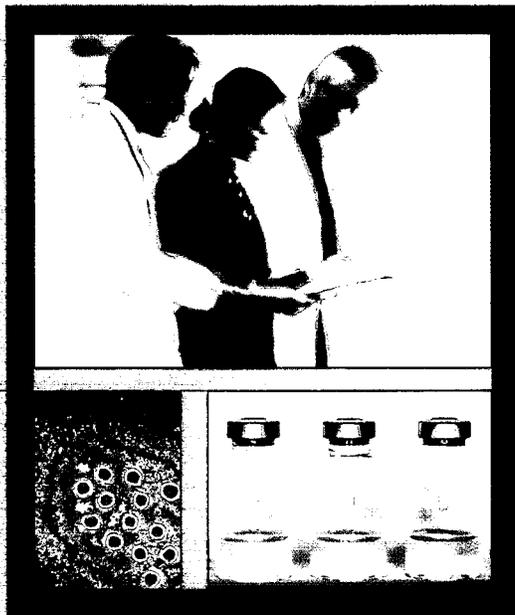




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# Pipeline 2004

PROGRAMS/PRODUCTS <sup>(1)</sup>	DISCOVERY	LEAD COMPOUND OPTIMIZATION	PRE-CLINICAL	PHASE I	PHASE II	PHASE III	MARKET	OUR COMMERCIAL RIGHTS
Diabetes CS-917	DEVELOPMENT UNDER REVIEW <sup>(2)</sup>							Worldwide
Hepatitis B TMC-95	DEVELOPMENT UNDER REVIEW <sup>(2)</sup>							Worldwide
Primary Liver Cancer MB07803	DEVELOPMENT UNDER REVIEW <sup>(2)</sup>							Worldwide
Diabetes MB07803	DEVELOPMENT ON HOLD <sup>(4)</sup>							Worldwide
Hyperlipidemia MB07811	DEVELOPMENT ON HOLD <sup>(4)</sup>							Worldwide
Diabetes/Hyperlipidemia Unlabeled	DEVELOPMENT ON HOLD <sup>(4)</sup>							Worldwide
Hepatitis C Unlabeled	DEVELOPMENT ON HOLD <sup>(4)</sup>							Worldwide
Liver Fibrosis MB07804	DEVELOPMENT ON HOLD <sup>(4)</sup>							Worldwide

- (1) None of our product candidates have received regulatory approval in the U.S. or in foreign countries.
- (2) This is the lead compound we are currently studying in our advanced research program for the treatment of the disease listed.
- (3) We are collaborating with Merck to apply our HepDirect<sup>™</sup> technology to certain compounds Merck has studied for the treatment of hepatitis C infection.
- (4) CS-917 and MB07803 diabetes programs are currently under review due to certain safety issues. Please refer to the accompanying Form 10-K for further information.

## Letter to Shareholders

Paul K. Laikind, Ph.D.  
Chairman of the Board  
Chief Executive Officer  
and President

### DEAR SHAREHOLDERS,

In this, our inaugural letter to shareholders since becoming a public company, I am pleased to report that Metabasis Therapeutics made excellent progress in 2004 toward our goal of building a world-class, fully integrated pharmaceutical company focused on providing important new medicines for debilitating, often life-threatening diseases. We advanced our product pipeline, continued to gain scientific recognition for our drug candidates and technology platforms, and took important steps to strengthen the Company, including the completion of an initial public offering in June 2004 and the addition of key members to our board of directors and management team.

Recently we faced a challenge to our development-stage diabetes program. On March 15, 2005, we were notified by our partner Sankyo Co., Ltd. that two serious adverse events had occurred during a clinical trial of CS-917, our first-in-class oral treatment for type II diabetes. Specifically, two patients had lactic acidosis in a drug interaction clinical trial that involved co-administration of CS-917 with the marketed diabetes drug metformin. The serious adverse events were resolved after medical intervention; however, this finding resulted in the halting of three clinical trials and a review of the future of the CS-917 development program. As this letter is written, we are working diligently to understand the implications of this news and determine the future of this drug candidate. As we work through these issues, we will continue to focus on our product pipeline to move our drug candidates through clinical trials as quickly as possible with the goal of delivering important new drugs to patients around the world.

### PIPELINE PROGRESS

We began 2004 with three products in clinical trials, and we ended the year having demonstrated promising evidence of efficacy for two of these drug candidates – CS-917 and pradefovir, our HepDirect antiviral agent for treating hepatitis B. We are continuing to evaluate our third clinical-stage compound, MB07133, for the treatment of primary liver cancer in a clinical study that involves treatment of patients with the disease.

We are also working to add new candidates to our product pipeline. One such candidate is MB07803, a treatment for diabetes in the same class as CS-917. MB07803 is nearly ready to enter clinical trials; however, it is also on hold pending decisions regarding CS-917. In addition, if all goes according to plan, we expect to soon recommend our fifth internally discovered candidate for clinical development – a compound with potential for treating hyperlipidemia and possibly obesity. We also continue to develop another novel approach to treating diabetes and metabolic syndrome. Finally, we are making good progress in our collaboration with Merck & Co., Inc. aimed at finding new treatments for hepatitis C.

### PRODUCT CANDIDATE UPDATE

#### *CS-917 – First-in-Class Oral Gluconeogenesis Inhibitor for the Treatment of Type II Diabetes*

New approaches to treating type II diabetes, a disease afflicting about 160 million people worldwide, are desperately needed since current therapeutic options are often insufficient to reduce blood glucose to the level recommended by the American Diabetes Association and prevent the onset of debilitating and often life-threatening diabetic complications. We believe that CS-917, discovered using our proprietary NuMimetic™ technology, is the first product candidate to enter clinical trials that is designed to directly inhibit a metabolic pathway in the liver responsible for producing glucose. By inhibiting this pathway, CS-917 reduces liver glucose production. In September 2004, we made several presentations at the 40th Annual Meeting of the European Association for the Study of Diabetes highlighting the unique mechanism of action of CS-917 and its performance in preclinical models of type II diabetes.

We are developing CS-917 in collaboration with Sankyo, a leading Japanese pharmaceutical company. Two Phase II clinical trials, which evaluated the drug administered as a single agent in type II diabetics including a 28-day clinical trial that was completed in 2004, demonstrated that CS-917 is capable of significantly lowering blood glucose levels and is safe and well tolerated. Additional clinical trials were conducted, and a three-month dose-ranging clinical trial designed to select a dose for the pivotal Phase III trials was initiated in December 2004. As of March 15, 2005, these clinical trials have been halted as a result of the serious adverse events that occurred in the combination clinical trial described above and the future of the CS-917 development program is under review.

*Pradefovir – HepDirect Liver-Targeted Antiviral for the Treatment of Hepatitis B*

Hepatitis B is the most common serious liver infection in the world. Two billion individuals have been infected with the hepatitis B virus (HBV) worldwide (one out of three people); about one million people die from the disease each year, and 350 million are struggling with chronic infection, including 1.2 million Americans. Pradefovir employs our proprietary HepDirect prodrug technology and is designed to deliver a proven antiviral agent, adefovir, specifically to the liver while limiting the amount of the active agent in the blood and other organs. Consequently, we believe that pradefovir may improve the efficacy of adefovir by reducing its side effects.

The development of pradefovir moved ahead strongly in 2004. Our partner, Valeant Pharmaceuticals, Ltd., completed two 28-day double-blind, placebo-controlled clinical trials in patients with hepatitis B in the United States and Asia showing that pradefovir effectively reduced viral load. The findings from the Asian study were presented at the 2004 annual meeting of the American Association for the Study of Liver Diseases last November. In this study, four dose groups were tested and each showed a clinically significant reduction, up to over 500-fold, of hepatitis B virus in patients treated with pradefovir, compared to patients treated with a placebo. Moreover, the drug was well tolerated, and the plasma levels of

adefovir were consistent with expectations for the HepDirect prodrug. After reviewing these promising results, Valeant launched a Phase II dose-ranging clinical trial and completed enrollment before the end of the year. The activity of the drug in this clinical trial will be evaluated after six months; the dose will be selected for Phase III testing, and, if the data supports proceeding, a Phase III trial will be initiated.

*MB07133 – HepDirect Liver-Targeted Oncolytic for the Treatment of Primary Liver Cancer*

Primary liver cancer (malignancy that starts in the liver) is the fifth most common cancer in the world, with approximately 550,000 new cases reported every year. A strong relationship exists between liver cancer and chronic hepatitis B and hepatitis C infection. The current worldwide epidemic of hepatitis C is expected to fuel a dramatic increase in primary liver cancer. Unfortunately, this devastating disease is one of the few cancers that currently lack an FDA-approved drug treatment.

MB07133 uses our HepDirect technology to target the active form of a well known cancer drug called cytarabine, or araC, to the liver. Cytarabine is often used as first-line therapy for leukemia, but is not effective in treating solid tumors such as those found in primary liver cancer. The HepDirect technology allows us to deliver an effective form of cytarabine to the liver, bypassing a known resistance mechanism. Multiple preclinical studies have shown that this unique liver-targeting property also results in decreased drug levels in tissues outside the liver, leading us to expect that MB07133 may help minimize the toxicities normally associated with cytarabine.

We retain all rights to MB07133 and have been studying it in a Phase I clinical trial in patients with primary liver cancer for the past year at sites in the United States, Hong Kong and Taiwan to determine the maximum safe and well tolerated dose. We then intend to conduct a small study to evaluate indicators of efficacy. With these data in hand, we plan to meet with the U.S. Food and Drug Administration (FDA) to determine a clinical development pathway for the drug. Given the life-threatening nature of the disease and the lack of effective treatment, we hope that an accelerated approval strategy might be available.

*MB07803 – Second-Generation Oral Gluconeogenesis Inhibitor for the Treatment of Type II Diabetes*

Our experience with CS-917 encouraged us to develop a second-generation product with the same mechanism of action. Called MB07803, this compound is designed to provide a meaningful and marketable improvement over CS-917. Rather than supplanting CS-917, we believe that MB07803, if approved, would help to expand the market for this new category of diabetes treatment. Metabasis currently retains all rights to MB07803 worldwide. MB07803 is nearly ready to enter clinical trials; however, further development has been suspended pending the review of CS-917.

**LEVERAGING OUR PROPRIETARY TECHNOLOGIES**

Metabasis has developed several unique, proprietary technologies that we are using to build a robust product pipeline. Our NuMimetic technology encompasses our expertise in targeting specific regulatory sites on certain key enzymes that control important metabolic pathways. We have successfully employed this technology to discover both CS-917 and MB07803, and are currently using it in an exciting program focused on a novel treatment for diabetes that acts via a mechanism completely different from CS-917 and MB07803.

Our HepDirect prodrug technology is designed to target drugs directly to the liver. This versatile technology has allowed us to put two products into clinical trials, pradefovir and MB07133. We are also applying it in other programs, including a project that may soon provide us with a promising development candidate for treating hyperlipidemia and possibly obesity. In addition, we are working with Merck to apply our HepDirect technology as well as other proprietary liver-targeting technologies to improve the safety and efficacy of compounds provided by Merck with the goal of developing new treatments for hepatitis C. If successful, we would receive milestone payments from Merck and share in the profit from product sales. Several papers on our HepDirect technology appeared in prestigious journals during the past year, including a brief review in the journal *Nature* that highlighted the potential importance of this novel technology.

Finally, Metabasis has developed proprietary technology related to computer-assisted drug design. This work has already helped us to succeed in many of our current programs, and we expect it to continue to contribute to our future success.

**MARCH TO COMMERCIALIZATION**

Thanks to our smart and effective research and development group we are building a pipeline of potential products. We are increasingly focused on the clinical development and eventual commercialization of our product candidates. Once our products are approved, we intend to directly market some of them ourselves through a specialized sales force. To that end, we have retained commercial rights, either worldwide rights or co-promotion rights in North America, to all of our metabolic product candidates and to our cancer product candidate.

As our product candidates advance, we continue to build our corporate infrastructure. We took important steps in that direction last year when we added Mr. Bill Rohn, previously Chief Operating Officer at Biogen Idec, and Mr. Dan Burgess, Chief Operating Officer at Hollis-Eden Pharmaceuticals, Inc., to our board of directors. In addition, we recently expanded our management team with the appointments of John Lucas, Ph.D., J.D., as Vice President of Intellectual Property, and Julie Cunningham as Vice President of Investor Relations and Corporate Communications.

In closing, I want to thank all of you for your support as we have pursued our goal of becoming a world-class, fully integrated pharmaceutical company that develops important new medicines and provides a significant return to shareholders. The path a drug takes to market is seldom without obstacles and the same is true for the path a company follows to success. We have clearly hit an obstacle in our diabetes program and we now need to determine how we navigate around it. On behalf of the entire Metabasis team, I can assure you that we remain committed to our mission and confident about our future.

Sincerely



*Paul K. Laikind, Ph.D.*

*Chairman, Chief Executive Officer and President*

# Corporate Directory

## CORPORATE MANAGEMENT

Paul K. Laikind, Ph.D.  
Chairman, Chief Executive Officer  
and President

Mark D. Erion, Ph.D.  
Executive Vice President, Research  
and Development, Director

John W. Beck, CPA  
Sr. Vice President of Finance,  
Chief Financial Officer and Treasurer

Edgardo Baracchini, Ph.D., M.B.A.  
Sr. Vice President, Business Development

John M. Lucas, Ph.D., J.D.  
Vice President, Intellectual Property

Julie C. Cunningham  
Vice President, Investor Relations  
and Corporate Communications

## BOARD OF DIRECTORS

Paul K. Laikind, Ph.D.  
Chairman, Chief Executive Officer  
and President

Mark D. Erion, Ph.D.  
Executive Vice President,  
Research and Development, Director

Daniel D. Burgess  
Chief Operating Officer,  
Chief Financial Officer,  
Hollis-Eden Pharmaceuticals, Inc.

Luke B. Evin, Ph.D.  
General Partner  
MPM Capital

Heinz W. Gschwend, Ph.D.  
Independent Consultant

David F. Hale  
President and Chief Executive Officer  
CancerVax Corporation

Arnold L. Oronsky, Ph.D.  
General Partner  
InterWest Partners

William R. Rohn  
Independent Consultant

## SCIENTIFIC ADVISORY BOARD

D. Montgomery Bissell, M.D.  
Professor of Medicine,  
Director of the Division of  
Gastroenterology at the University of  
California, San Francisco

Alan Cherrington, Ph.D.  
Professor and Chair of the Department of  
Molecular Physiology and Biophysics at  
Vanderbilt University

Anna Mae Diehl, M.D.  
Chief of Gastroenterology,  
Duke University

Jules Dienstag, M.D.  
Associate Professor of Medicine at Harvard  
Medical School, and Physician at  
Massachusetts General Hospital

Heinz W. Gschwend, Ph.D.  
Independent Consultant

David J. H. Herzig, Ph.D.  
Independent Consultant

Gerald I. Shulman, M.D., Ph.D.  
Investigator of the Howard Hughes Medi-  
cal Institute and Professor of Medicine and  
Cellular & Molecular Physiology at  
Yale University School of Medicine

Alan Venook, M.D.  
Professor of Clinical Medicine,  
Director of the Clinical Research Office in  
the UCSF Cancer Center

David J. Waxman, Ph.D.  
Professor of Cell and Molecular Biology  
at Boston University and Professor of  
Medicine at Boston University School of  
Medicine

## CORPORATE COUNSEL

Cooley Godward LLP  
4401 Eastgate Mall  
San Diego, CA 92121

## INDEPENDENT ACCOUNTANTS

Ernst & Young LLP  
501 West Broadway, Suite 1100  
San Diego, CA 92101

## ANNUAL STOCKHOLDERS MEETING

The annual report and proxy statement will be mailed by April 25, 2005. Metabasis' annual meeting of stockholders will be held at 10:00 am Pacific Time on Wednesday, May 18, 2005 at:

San Diego Marriott, La Jolla  
4240 La Jolla Village Drive  
La Jolla, CA 92037

## COMMON STOCK INFORMATION

On March 1, 2005 there were approximately 18,180,482 shares of Metabasis common stock outstanding and approximately 121 stockholders of record. Metabasis common stock is traded on the NASDAQ National Market under the symbol "MBRX".

## COMPANY CONTACT

Julie Cunningham  
Vice President, Investor Relations  
and Corporate Communications  
858-587-2770  
ir@mbasis.com

## REGISTRAR AND TRANSFER AGENT

American Stock Transfer  
& Trust Company  
59 Maiden Lane  
Plaza Level  
New York, NY 10038  
800-937-5449

## QUARTERLY REPORTING AND OTHER INFORMATION

Metabasis' current quarterly reports, annual reports, other SEC filings, news releases and other information regarding the Company and its technology are available on the Internet: [www.mbasis.com](http://www.mbasis.com)

## FORM 10-K

A copy of the Company's Form 10-K, which is filed with the Securities and Exchange Commission, is available upon request, free of charge. Write to:

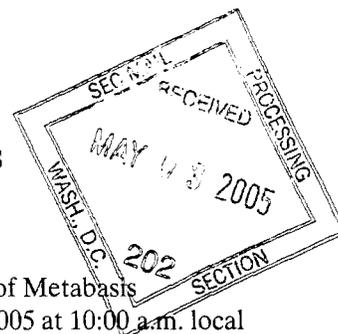
Metabasis Therapeutics, Inc.  
Attention: Investor Relations Department  
9390 Towne Centre Drive, Bldg. 300  
San Diego, CA 92121  
Phone: 858-587-2770  
[www.mbasis.com](http://www.mbasis.com)

## SAFE HARBOR STATEMENT

This annual report includes forward-looking statements that are based on our management's current beliefs and assumptions and on information currently available to our management. 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. Please see the sections entitled "Risk Factors" and "Forward-Looking Statements" in the accompanying Form 10-K for a more detailed description of these risks and uncertainties as well as additional information regarding forward looking statements.

**METABASIS THERAPEUTICS, INC.**  
9390 Towne Centre Drive, Building 300  
San Diego, California 92121

**NOTICE OF ANNUAL MEETING OF STOCKHOLDERS  
TO BE HELD ON MAY 18, 2005**



Dear Stockholder:

You are cordially invited to attend the 2005 Annual Meeting of Stockholders of Metabasis Therapeutics, Inc., a Delaware corporation. The meeting will be held on May 18, 2005 at 10:00 a.m. local time at the San Diego Marriott, La Jolla, located at 4240 La Jolla Village Drive, La Jolla, CA 92037, for the following purposes:

1. To elect two Class I directors to hold office until our 2008 Annual Meeting of Stockholders.
2. To ratify the selection by the Audit Committee of our Board of Directors of Ernst & Young LLP as our independent auditors for the fiscal year ending December 31, 2005.
3. To conduct any other business properly brought before the meeting.

These items of business are more fully described in the proxy statement accompanying this notice.

The record date for the annual meeting is April 11, 2005. Only stockholders of record at the close of business on that date may vote at the meeting or any adjournment or postponement thereof.

By Order of the Board of Directors

Paul K. Laikind, Ph.D.  
*Chairman of the Board, Chief Executive Officer,  
President and Secretary*

San Diego, California  
April 25, 2005

**You are cordially invited to attend the meeting in person. Whether or not you expect to attend the meeting, please complete, date, sign and return the proxy accompanying this notice as promptly as possible in order to ensure your representation at the meeting. A return envelope (which is postage prepaid if mailed in the United States) is enclosed for your convenience. Even if you have voted by proxy, you may still vote in person if you attend the meeting. Please note, however, that if your shares are held of record by a broker, bank or other agent and you wish to vote at the meeting, you must request and obtain a proxy issued in your name from that record holder.**

**METABASIS THERAPEUTICS, INC.**  
9390 Towne Centre Drive, Building 300  
San Diego, California 92121

**PROXY STATEMENT  
FOR THE ANNUAL MEETING OF STOCKHOLDERS  
TO BE HELD MAY 18, 2005**

**QUESTIONS AND ANSWERS**

**Why am I receiving these proxy materials?**

We sent you this proxy statement and the accompanying proxy card because the Board of Directors of Metabasis Therapeutics, Inc. is soliciting your proxy to vote at its 2005 Annual Meeting of Stockholders. You are invited to attend the annual meeting to vote on the proposals described in this proxy statement. However, you do not need to attend the meeting to vote your shares. Instead, you may simply complete, sign and return the accompanying proxy card.

We intend to mail this proxy statement and the accompanying proxy card on or about April 25, 2005 to all stockholders of record entitled to vote at the annual meeting.

**Who can vote at the annual meeting?**

Only stockholders of record at the close of business on April 11, 2005, the record date for the annual meeting, will be entitled to vote at the annual meeting. At the close of business on the record date, there were 18,183,283 shares of common stock outstanding and entitled to vote.

*Stockholder of Record: Shares Registered in Your Name*

If at the close of business on the record date, your shares were registered directly in your name with our transfer agent, American Stock Transfer & Trust Company, then you are a stockholder of record. As a stockholder of record, you may vote in person at the meeting or vote by proxy. Whether or not you plan to attend the meeting, we urge you to fill out and return the accompanying proxy card to ensure your vote is counted.

*Beneficial Owner: Shares Registered in the Name of a Broker, Bank or Other Agent*

If at the close of business on the record date, your shares were held, not in your name, but rather in an account at a brokerage firm, bank or other agent, then you are the beneficial owner of shares held in "street name" and these proxy materials are being forwarded to you by your broker, bank or other agent. The broker, bank or other agent holding your account is considered to be the stockholder of record for purposes of voting at the annual meeting.

As a beneficial owner, you have the right to direct your broker, bank or other agent on how to vote the shares in your account. You are also invited to attend the annual meeting. However, since you are not the stockholder of record, you may not vote your shares in person at the meeting unless you request and obtain a valid proxy issued in your name from your broker, bank or other agent.

**What am I voting on?**

There are two matters scheduled for a vote at the annual meeting:

- the election of two Class I directors to hold office until our 2008 Annual Meeting of Stockholders, and
- the ratification of the selection by the Audit Committee of our Board of Directors of Ernst & Young LLP as our independent auditors for the fiscal year ending December 31, 2005.

**How do I vote?**

For the election of directors, you may either vote "For" both nominees or you may "Withhold" your vote for any nominee you specify. For any other matter to be voted on, you may vote "For" or "Against" or abstain from voting. The procedures for voting are as follows:

*Stockholder of Record: Shares Registered in Your Name*

If you are a stockholder of record, you may vote in person at the annual meeting. Alternatively, you may vote by proxy by using the accompanying proxy card. Whether or not you plan to attend the meeting, we urge you to vote by proxy to ensure your vote is counted. You may still attend the meeting and vote in person if you have already voted by proxy.

- To vote in person, come to the annual meeting and we will give you a ballot when you arrive.
- To vote using the proxy card, simply complete, sign and date the accompanying proxy card and return it promptly in the envelope provided. If you return your signed proxy card to us before the annual meeting, we will vote your shares as you direct.

*Beneficial Owner: Shares Registered in the Name of Broker, Bank or Other Agent*

If you are a beneficial owner of shares registered in the name of your broker, bank or other agent, you should have received a proxy card and voting instructions with these proxy materials from that organization rather than from us. Simply complete and mail the proxy card to ensure that your vote is counted. To vote in person at the annual meeting, you must obtain a valid proxy from your broker, bank or other agent. Follow the instructions from your broker, bank or other agent included with these proxy materials, or contact your broker, bank or other agent to request a proxy form.

**How many votes do I have?**

On each matter to be voted upon, you have one vote for each share of common stock you own as of the close of business on April 11, 2005, the record date for the annual meeting.

**What if I return a proxy card but do not make specific choices?**

If you return a signed and dated proxy card without marking any voting selections, your shares will be voted "For" the election of both nominees for director and "For" the ratification of the selection of Ernst & Young LLP as our independent auditors. If any other matter is properly presented at the meeting, one of the individuals named on your proxy card as your proxy will vote your shares using his or her best judgment.

**Who is paying for this proxy solicitation?**

We will pay for the entire cost of soliciting proxies. In addition to these mailed proxy materials, our directors and employees may also solicit proxies in person, by telephone, or by other means of communication. Directors and employees will not be paid any additional compensation for soliciting proxies. We may also reimburse brokerage firms, banks and other agents for the cost of forwarding proxy materials to beneficial owners.

**What does it mean if I receive more than one proxy card?**

If you receive more than one proxy card, your shares are registered in more than one name or are registered in different accounts. Please complete, sign and return each proxy card to ensure that all of your shares are voted.

**Can I change my vote after submitting my proxy?**

Yes. You can revoke your proxy at any time before the applicable vote at the meeting. If you are the record holder of your shares, you may revoke your proxy in any one of three ways:

- you may submit another properly completed proxy with a later date,
- you may send a written notice that you are revoking your proxy to our Secretary at 9390 Towne Centre Drive, Building 300, San Diego, California 92121, or
- you may attend the annual meeting and vote in person (however, simply attending the meeting will not, by itself, revoke your proxy).

If your shares are held by your broker, bank or other agent, you should follow the instructions provided by them.

**When are stockholder proposals due for next year's annual meeting?**

To be considered for inclusion in next year's proxy materials, a stockholder proposal must be submitted in writing by December 26, 2005, to our Secretary at 9390 Towne Centre Drive, Building 300, San Diego, California 92121. If you wish to submit a proposal that is not to be included in next year's proxy materials, your proposal generally must be submitted in writing to the same address no later than February 17, 2006 but no earlier than January 18, 2006. Please review our bylaws, which contain additional requirements regarding advance notice of stockholder proposals.

**How are votes counted?**

Votes will be counted by the inspector of election appointed for the meeting, who will separately count "For" and "Withhold" and, with respect to any proposals other than the election of directors, "Against" votes, abstentions and broker non-votes. A "broker non-vote" occurs when a nominee holding shares for a beneficial owner does not vote on a particular proposal because the nominee does not have discretionary voting power with respect to that proposal and has not received instructions with respect to that proposal from the beneficial owner, despite voting on at least one other proposal for which it does have discretionary authority or for which it has received instructions. Abstentions will be counted towards the vote total for each proposal, and will have the same effect as "Against" votes. Broker non-votes have no effect and will not be counted towards the vote total for any proposal.

If your shares are held by your broker, bank or other agent as your nominee (that is, in "street name"), you will need to obtain a proxy form from the institution that holds your shares and follow the instructions included on that form regarding how to instruct your broker, bank or other agent to vote your shares. If you do not give instructions to your broker, bank or other agent, they can vote your shares with

respect to “discretionary” items, but not with respect to “non-discretionary” items. Discretionary items are proposals considered routine under the rules of the New York Stock Exchange on which your broker, bank or other agent may vote shares held in street name in the absence of your voting instructions. On non-discretionary items for which you do not give instructions to your broker, bank or other agent, the shares will be treated as broker non-votes.

**How many votes are needed to approve each proposal?**

- For the election of directors, the two nominees receiving the most “For” votes (among votes properly cast in person or by proxy) will be elected. Only votes “For” or “Withheld” will affect the outcome.
- To be approved, the ratification of the selection of Ernst & Young LLP as our independent auditors must receive a “For” vote from the majority of shares present and entitled to vote either in person or by proxy.

**What is the quorum requirement?**

A quorum of stockholders is necessary to hold a valid meeting. A quorum will be present if at least a majority of the outstanding shares as of the close of business on the record date are represented by stockholders present at the meeting or by proxy. At the close of business on the record date, there were 18,183,283 shares outstanding and entitled to vote. Therefore, in order for a quorum to exist, 9,091,642 shares must be represented by stockholders present at the meeting or by proxy.

Your shares will be counted towards the quorum only if you submit a valid proxy (or one is submitted on your behalf by your broker, bank or other agent) or if you vote in person at the meeting. Abstentions and broker non-votes will be counted towards the quorum requirement. If there is no quorum, a majority of the votes present at the meeting may adjourn the meeting to another date.

**How can I find out the results of the voting at the annual meeting?**

Preliminary voting results will be announced at the annual meeting. Final voting results will be published in our Quarterly Report on Form 10-Q for the second quarter of 2005.

**PROPOSAL 1**  
**ELECTION OF DIRECTORS**

Our Board of Directors currently consists of eight members and is divided into three classes, each of which has a three-year term. Class I consists of two directors and Classes II and III consist of three directors each. The Class I directors are to be elected at the annual meeting to serve until our 2008 Annual Meeting of Stockholders and until their successors are duly elected and qualified, or until their death, resignation or removal. The terms of the directors in Classes II and III expire at our 2006 and 2007 Annual Meetings of Stockholders, respectively.

The two nominees for Class I directors are Daniel D. Burgess, M.B.A. and Luke B. Evnin, Ph.D. Each of the nominees is currently a director of Metabasis. Neither of the nominees was elected by our stockholders, as both were previously appointed by our Board of Directors prior to our initial public offering to fill a vacancy then existing on the Board. Mr. Burgess's original nomination was recommended prior to our initial public offering by our Chief Executive Officer in consultation with other members of our Board of Directors and Dr. Evnin's original nomination was recommended prior to our initial public offering by the former holders of our Series C preferred stock pursuant to a right to board representation formerly contained in our Certificate of Incorporation. This board representation right terminated upon the completion of our initial public offering in June 2004.

Directors are elected by a plurality of the votes present at the meeting or by proxy and entitled to vote at the meeting. The two nominees receiving the most "For" votes (among votes properly cast in person or by proxy) will be elected. If no contrary indication is made, shares represented by executed proxies will be voted "For" the election of the two nominees named above or, if either nominee becomes unavailable for election as a result of an unexpected occurrence, "For" the election of a substitute nominee designated by our Board of Directors. Each nominee has agreed to serve as a director if elected, and we have no reason to believe that any nominee will be unable to serve.

We encourage all of our directors and nominees for director to attend our annual meeting of stockholders. We did not hold an annual meeting of stockholders during the fiscal year ended December 31, 2004.

**THE BOARD OF DIRECTORS RECOMMENDS A VOTE FOR THE ELECTION OF EACH NOMINEE NAMED ABOVE.**

The following is biographical information as of March 1, 2005 for each nominee for Class I director and each person whose term of office as a Class II or III director will continue after the annual meeting.

<u>Name</u>	<u>Age</u>	<u>Position</u>
Daniel D. Burgess, M.B.A. ....	43	Director
Mark D. Erion, Ph.D.....	47	Executive Vice President of Research and Development and Director
Luke B. Evnin, Ph.D. ....	41	Director
Heinz W. Gschwend, Ph.D.....	69	Director
David F. Hale .....	56	Director
Paul K. Laikind, Ph.D.....	49	Chairman of the Board, Chief Executive Officer, President and Secretary
Arnold L. Oronsky, Ph.D.....	64	Director
William R. Rohn.....	61	Director

**Nominees for Election for a Three-year Term Expiring at the 2008 Annual Meeting**

*Daniel D. Burgess, M.B.A.* has served on our Board of Directors since March 2004. Mr. Burgess has been the Chief Operating Officer and Chief Financial Officer of Hollis-Eden Pharmaceuticals, Inc. since

August 1999. Mr. Burgess joined Hollis-Eden from Nanogen, Inc., where he served as Vice President and Chief Financial Officer. Prior to joining Nanogen in 1998, Mr. Burgess spent ten years with Gensia, Inc., including with Gensia Automedics, Inc., a partially owned subsidiary of Gensia. Mr. Burgess served as President and a director of Gensia Automedics, where he was responsible for all functional areas of this medical products company. In addition, he was Vice President and Chief Financial Officer of Gensia, where he was responsible for finance, investor relations, business development and other administrative functions. Prior to joining Gensia, Mr. Burgess held positions at Castle & Cooke, Inc. and Smith Barney, Harris Upham and Company. Mr. Burgess is also a director of Santarus, Inc., a publicly-held specialty pharmaceutical company. He received a degree in economics from Stanford University and an M.B.A. from Harvard Business School.

*Luke B. Evinin, Ph.D.* has served on our Board of Directors since September 2000. Dr. Evinin is a General Partner at MPM Capital, a venture capital firm focusing on global healthcare investments. Before joining MPM Capital in 1998, Dr. Evinin was affiliated with Accel Partners for seven years, including four years as a General Partner. He was involved in biopharmaceutical, pharmaceutical, medical device and healthcare service companies for Accel Partners' funds III, IV, and V. He was responsible for overall investment strategy, deal origination, analyses, investment and gain realization. Dr. Evinin serves on the board of directors of the publicly-held biopharmaceutical company Oscient Pharmaceuticals Corporation as well as several privately-held healthcare companies, including BioValve Technologies, Inc. He also serves on the board of directors of Medical Portfolio Management, L.P., an investment management firm, and is chairman of the Scleroderma Research Foundation. Dr. Evinin holds a Ph.D. in biochemistry from the University of California at San Francisco, and an A.B. in Molecular Biology from Princeton University.

#### **Directors Continuing in Office Until the 2006 Annual Meeting**

*Mark D. Erion, Ph.D.* is one of our founders and has served as our Executive Vice President of Research and Development since April 1997 and on our Board of Directors since June 1999. Prior to joining Metabasis, Dr. Erion was with Gensia, where he served as Director of Chemistry and Biochemistry from 1991 and assumed responsibility for research in 1996. Prior to joining Gensia, Dr. Erion was a Group Leader at Ciba-Geigy Pharmaceutical Company, where he directed a team in the area of protein engineering. Dr. Erion's research has resulted in over 90 publications and 30 U.S. patents. His discovery efforts over the past 12 years have produced seven clinical candidates, several research collaborations and more recently our HepDirect and NuMimetic technologies. Dr. Erion received a B.S. in mathematics and chemistry from the University of Oregon, a Ph.D. in Chemistry from Cornell University and was a National Institutes of Health postdoctoral fellow in enzymology at the Massachusetts Institute of Technology.

*Arnold L. Oronsky, Ph.D.* has served on our Board of Directors since September 2000. Dr. Oronsky is a General Partner at InterWest Partners, a venture capital firm focusing on investments in life sciences and information technology. Dr. Oronsky joined InterWest Partners in a full-time capacity in 1994 after serving as a special limited partner since 1989. He also serves as a senior lecturer in the Department of Medicine at Johns Hopkins Medical School. From 1980 to 1993, Dr. Oronsky was Vice President for Discovery Research at the Lederle Laboratories division of American Cyanamid Company, a pharmaceutical company. From 1973 to 1976, Dr. Oronsky was Head of Inflammation, Allergy and Immunology Research at Ciba-Geigy. From 1970 to 1972, he was an assistant professor at Harvard Medical School, where he also served as a research fellow from 1968 to 1970. Dr. Oronsky serves on the board of directors of the publicly-held biotechnology companies Aspreva Pharmaceuticals, Inc., Corixa Corporation, Dynavax Technologies, Inc. and Myogen, Inc. He holds a Ph.D. from Columbia University, College of Physicians and Surgeons and a B.S. degree from University College, New York University.

*William R. Rohn* has served on our Board of Directors since December 2004. In January 2005, Mr. Rohn retired from Biogen Idec Inc., where he had served as Chief Operating Officer since the merger of IDEC Pharmaceuticals Inc. and Biogen, Inc. in November 2003. Mr. Rohn joined IDEC in August 1993

as Senior Vice President, Commercial and Corporate Development, was appointed Senior Vice President, Commercial Operations in April 1996 and was promoted to Chief Operating Officer in May 1998 and President in January 2002. Prior to joining IDEC, Mr. Rohn was employed by Adria Laboratories, now part of Pfizer, from 1984 until 1993, most recently as Senior Vice President of Sales and Marketing. Prior to Adria, Mr. Rohn held marketing and sales management positions at Abbott Laboratories, Warren-Teed Pharmaceuticals, Miles Laboratories and Mead Johnson Laboratories. Mr. Rohn serves on the Board of Directors of Cerus Corporation, a publicly-held biotechnology company, Pharmacyclics, Inc., a publicly-held pharmaceutical company, and Raven Biotechnologies, a privately-held biotechnology company. Mr. Rohn received a B.A. in Marketing from Michigan State University.

#### **Directors Continuing in Office Until the 2007 Annual Meeting**

*Heinz W. Gschwend, Ph.D.* has served on our Board of Directors and our scientific advisory board since August 1999. Dr. Gschwend has over 33 years of experience in pharmaceutical research, drug discovery and development. Since 1998, he has served as a consultant, scientific advisory board member and/or director for several biotechnology companies. From 1992 to 1997, he was with Arris Pharmaceuticals, where he played a leading role in building a successful discovery effort in the area of protease inhibition. From 1967 to 1991 he was with the Pharmaceuticals Division and Central Research Department of Ciba-Geigy in the U.S. and Switzerland, respectively. During his career at Ciba-Geigy he was involved in the discovery and development of over 80 pre-clinical and clinical product candidates. Two drugs from those efforts are marketed: Benazepril and Letrozole. Dr. Gschwend holds a Ph.D. degree in chemistry from the ETH, and conducted postdoctoral studies at the ETH and Harvard University.

*David F. Hale* has served on our Board of Directors since April 1997. Mr. Hale has served as President and Chief Executive Officer of CancerVax Corporation since October 2000 and as a director of CancerVax since December 2000. Prior to joining CancerVax, he was President and Chief Executive Officer and a director of Women First HealthCare, Inc. from January 1998 to May 2000. Mr. Hale served as President, Chief Executive Officer and Chairman of Gensia from May 1987 to November 1997. Prior to joining Gensia, Mr. Hale was President and Chief Executive Officer of Hybritech Inc. Mr. Hale serves on the board of directors of the publicly-held specialty pharmaceutical company Santarus, Inc. as well as several privately-held biotechnology companies, including Somaxon Pharmaceuticals, Inc., SkinMedica, Inc. and Verus, Inc. Mr. Hale also serves as a director of BIOCUM, the California Healthcare Institute, BIO, and the BIO Emerging Company Growth Section. He is chairman of the Executive Committee of CONNECT. Mr. Hale received a B.A. in biology and chemistry from Jacksonville State University.

*Paul K. Laikind, Ph.D.* is one of our founders and has served on our Board of Directors since April 1997, as our Chairman of the Board and Chief Executive Officer since April 1998, and as our President and Secretary since June 1999. From 1986 to 1999, Dr. Laikind founded and was Vice President of Business Development and a director at Gensia, where he was responsible for establishing major research and development corporate partnerships with leading U.S. and European companies including Marion Merrell Dow, Sandoz, Boehringer Mannheim, Pfizer and Sankyo. While at Gensia, Dr. Laikind founded Viagene, Inc., a biotechnology company acquired by Chiron, Inc. in 1995. Dr. Laikind holds a Ph.D. in chemistry from the University of California at San Diego, or UCSD, and has served as a research faculty member at the UCSD School of Medicine.

## Executive Officers

The following is biographical information as of March 1, 2005 for our executive officers not discussed above.

<u>Name</u>	<u>Age</u>	<u>Position</u>
John W. Beck, C.P.A.....	45	Senior Vice President of Finance, Chief Financial Officer and Treasurer
Edgardo Baracchini, Ph.D., M.B.A. .	45	Senior Vice President of Business Development

*John W. Beck, C.P.A.* is one of our founders and has served as our Vice President of Finance, Chief Financial Officer and Treasurer since June 1999 and was promoted to our Senior Vice President of Finance, Chief Financial Officer and Treasurer in April 2005. Mr. Beck previously served as our Director of Finance from April 1998 to June 1999. Mr. Beck has more than 17 years of financial management experience. In February 1994 he joined Neurocrine Biosciences, Inc., where he served as Director of Finance from May 1996 to April 1998 and played an important role in Neurocrine's 1996 initial public offering. Prior to joining Neurocrine, Mr. Beck held financial management positions at high technology and financial services companies including General Dynamics and Ernst and Young LLP. Mr. Beck received a B.A. in accounting from the University of Washington and also holds a Th.B. in theology from a Seattle, Washington-based seminary. Mr. Beck is a licensed certified public accountant in the state of California and is a member of the American Institute of Certified Public Accountants and the Association of Bioscience Financial Officers.

*Edgardo Baracchini, Ph.D., M.B.A.* has served as our Vice President of Business Development since May 2002 and was promoted to our Senior Vice President of Business Development in April 2005. Dr. Baracchini has over ten years' experience in structuring and negotiating research and development partnerships, mergers and acquisitions, and in-licensing arrangements with leading pharmaceutical and biotechnology companies including Merck, Novo Nordisk, Roche, LG Chem, Boehringer Ingelheim, Zeneca, Incyte Genomics, Medichem, Trega, Axys, Inhale Therapeutics and ICOS. Prior to joining Metabasis, since 1999 Dr. Baracchini was an officer and Vice President of Business Development at Elitra Pharmaceuticals. From 1996 to 1999, Dr. Baracchini served as the Director of Business Development at Agouron Pharmaceuticals, and as Assistant Director of Business Development at Isis Pharmaceuticals from 1992 to 1996. Dr. Baracchini holds a Ph.D. in molecular and cell biology from the University of Texas at Dallas, an M.B.A. from the University of California, Irvine and a B.S. degree in microbiology from the University of Notre Dame.

## Independence of the Board of Directors and its Committees

As required under Nasdaq Stock Market listing standards, a majority of the members of a listed company's board of directors must qualify as "independent," as affirmatively determined by the board. Our Board of Directors consults with our counsel to ensure that the Board's determinations are consistent with all relevant securities and other laws and regulations regarding the definition of "independent," including those set forth in applicable Nasdaq listing standards, as in effect from time to time.

Consistent with these considerations, after review of all relevant transactions or relationships between each director, or any of his or her family members, and Metabasis, our senior management and our independent auditors, our Board of Directors has affirmatively determined that all of our directors are independent directors within the meaning of the applicable Nasdaq listing standards, except for Dr. Laikind, our Chairman of the Board, Chief Executive Officer, President and Secretary, and Dr. Erion, our Executive Vice President of Research and Development.

As required under applicable Nasdaq listing standards, our independent directors meet in regularly scheduled executive sessions at which only independent directors are present. All of the committees of our

Board of Directors are comprised entirely of directors determined by the Board to be independent within the meaning of the applicable Nasdaq listing standards.

**Information Regarding the Board of Directors and its Committees**

Our Board of Directors has an Audit Committee, a Compensation Committee and a Corporate Governance and Nominating Committee. The following is membership and meeting information for each of these committees during the fiscal year ended December 31, 2004, as well as a description of each committee and its functions.

<u>Name</u>	<u>Audit Committee</u>	<u>Compensation Committee</u>	<u>Corporate Governance and Nominating Committee</u>
Daniel D. Burgess, M.B.A. ....	X*		
Mark D. Erion, Ph.D. ....			
Luke B. Evnin, Ph.D. ....			X
Heinz W. Gschwend, Ph.D. ....		X	X
David F. Hale ....	X	X	X
Paul K. Laikind, Ph.D. ....			
Arnold L. Oronsky, Ph.D. ....	X	X*	
William R. Rohn. ....			
Total meetings in fiscal year 2004 .....	6	2	—

\* Committee Chairperson

*Audit Committee*

The Audit Committee operates pursuant to a written charter that is available on our website at <http://www.mbasis.com> and is attached as Appendix A to this proxy statement. The functions of the Audit Committee include, among other things:

- reviewing and pre-approving the engagement of our independent auditors to perform audit services and any permissible non-audit services,
- reviewing our annual and quarterly financial statements and reports and discussing the statements and reports with our independent auditors and management,
- reviewing with our independent auditors and management significant issues that arise regarding accounting principles and financial statement presentation, and matters concerning the scope, adequacy and effectiveness of our financial controls, and
- establishing procedures for the receipt, retention and treatment of complaints received by us regarding financial controls, accounting or auditing matters.

Our Board of Directors has determined that Mr. Burgess qualifies as an “audit committee financial expert,” as defined in applicable Securities and Exchange Commission, or SEC, rules. The Board made a qualitative assessment of Mr. Burgess’s level of knowledge and experience based on a number of factors, including his formal education and experience as a chief financial officer for public companies.

### *Compensation Committee*

The Compensation Committee operates pursuant to a written charter that is available on our website at <http://www.mbasis.com>. The functions of the Compensation Committee include, among other things:

- determining the compensation and other terms of employment of our executive officers and reviewing and approving corporate performance goals and objectives relevant to such compensation,
- recommending to our Board of Directors the type and amount of compensation to be paid or awarded to Board members,
- evaluating and recommending to our Board of Directors the equity incentive plans, compensation plans and similar programs advisable for us, as well as modification or termination of existing plans and programs,
- establishing policies with respect to equity compensation arrangements, and
- reviewing and approving the terms of any employment agreements, severance arrangements, change-in-control protections and any other compensatory arrangements for our executive officers.

### *Corporate Governance and Nominating Committee*

The Corporate Governance and Nominating Committee operates pursuant to a written charter that is available on our website at <http://www.mbasis.com>. The functions of the Corporate Governance and Nominating Committee include, among other things:

- developing and maintaining a current list of the functional needs and qualifications of members of our Board of Directors,
- evaluating director performance on our Board of Directors and applicable committees of the Board and determining whether continued service on the Board is appropriate,
- interviewing, evaluating, nominating and recommending individuals for membership on our Board of Directors,
- evaluating nominations by stockholders of candidates for election to our Board of Directors,
- developing, reviewing and amending a set of corporate governance policies and principles, including a code of ethics,
- considering questions of possible conflicts of interest of directors as such questions arise, and
- recommending to our Board of Directors the establishment of such special committees as may be desirable or necessary from time to time in order to address ethical, legal, business or other matters that may arise.

The Corporate Governance and Nominating Committee believes that candidates for director should have certain minimum qualifications, including being able to read and understand basic financial statements, being over 21 years of age and having the highest personal integrity and ethics. The Corporate Governance and Nominating Committee also considers such factors as possessing relevant expertise upon which to be able to offer advice and guidance to management, having sufficient time to devote to our affairs, demonstrated excellence in his or her field, having the ability to exercise sound business judgment and having the commitment to rigorously represent the long-term interests of our stockholders. However, the Corporate Governance and Nominating Committee retains the right to modify these qualifications from time to time.

Candidates for director nominees are reviewed in the context of the current composition of our Board of Directors, our operating requirements and the long-term interests of our stockholders. In conducting this assessment, the Corporate Governance and Nominating Committee considers diversity, age, skills, and such other factors as it deems appropriate given the current needs of the Board and Metabasis, to maintain a balance of knowledge, experience and capability. In the case of incumbent directors whose terms of office are set to expire, the Corporate Governance and Nominating Committee reviews such directors' overall service to us during their term, including the number of meetings attended, level of participation, quality of performance, and any other relevant considerations. In the case of new director candidates, the Corporate Governance and Nominating Committee also determines whether the nominee must be independent for Nasdaq purposes, which determination is based upon applicable Nasdaq listing standards, applicable SEC rules and regulations and the advice of counsel, if necessary. The Corporate Governance and Nominating Committee then uses its network of contacts to compile a list of potential candidates, but may also engage, if it deems appropriate, a professional search firm. The Corporate Governance and Nominating Committee conducts any appropriate and necessary inquiries into the backgrounds and qualifications of possible candidates after considering the function and needs of our Board of Directors. The Corporate Governance and Nominating Committee meets to discuss and consider such candidates' qualifications and then selects a nominee for recommendation to the Board by majority vote. The Corporate Governance and Nominating Committee recently paid a fee of approximately \$83,000 to a third party to assist in the process of identifying Mr. Rohn as a director candidate.

The Corporate Governance and Nominating Committee will consider director candidates recommended by stockholders. The Corporate Governance and Nominating Committee does not intend to alter the manner in which it evaluates candidates, including the minimum criteria set forth above, based on whether or not the candidate was recommended by a stockholder or not. Stockholders who wish to recommend individuals for consideration by the Corporate Governance and Nominating Committee to become nominees for election to the Board at an annual meeting of stockholders must do so by delivering at least 120 days prior to the anniversary date of the mailing of the proxy statement for our last annual meeting of stockholders a written recommendation to the Corporate Governance and Nominating Committee at the following address: 9390 Towne Centre Drive, Building 300, San Diego, California 92121. Each submission must set forth: the name and address of the stockholder on whose behalf the submission is made; the number of our shares that are owned beneficially by such stockholder as of the date of the submission; the full name of the proposed candidate; a description of the proposed candidate's business experience for at least the previous five years; complete biographical information for the proposed candidate; and a description of the proposed candidate's qualifications as a director. To date, the Corporate Governance and Nominating Committee has not received a director nominee from a stockholder or stockholders holding more than five percent of our voting stock.

#### **Meetings of the Board of Directors and Board and Committee Member Attendance**

Our Board of Directors met 11 times during the last fiscal year. Each Board member attended 75% or more of the aggregate of the meetings of the Board and of the committees on which he served, held during the period for which he was a director or committee member, respectively.

#### **Stockholder Communications With The Board Of Directors**

Our Board of Directors has adopted a formal process by which our stockholders may communicate with the Board or individual directors. Information regarding this process is available on our website at <http://www.mbasis.com>.

### **CODE OF BUSINESS CONDUCT AND ETHICS**

We have adopted a Code of Business Conduct and Ethics that applies to all of our officers, directors and employees. The Code of Business Conduct and Ethics is available on our website at <http://www.mbasis.com>. If we make any substantive amendments to the Code of Business Conduct and Ethics or grant any waiver from a provision of the Code of Business Conduct and Ethics to any executive officer or director, we will promptly disclose the nature of the amendment or waiver on our website, as well as via any other means then required by Nasdaq listing standards or applicable law.

### **ACCOUNTING AND AUDITING MATTERS OPEN DOOR POLICY**

We have adopted an Accounting and Auditing Matters Open Door policy to facilitate the receipt, retention and treatment of complaints regarding accounting, internal accounting controls or auditing matters, as well as the confidential, anonymous submission by our employees of concerns regarding these matters. The Accounting and Auditing Matters Open Door Policy is available on our website at <http://www.mbasis.com>.

## PROPOSAL 2

### RATIFICATION OF SELECTION OF INDEPENDENT AUDITORS

The Audit Committee of our Board of Directors has engaged Ernst & Young LLP as our independent auditors for the fiscal year ending December 31, 2005 and is seeking ratification of such selection by our stockholders at the annual meeting. Ernst & Young LLP has audited our financial statements since 1997. Representatives of Ernst & Young LLP are expected to be present at the annual meeting. They will have an opportunity to make a statement if they so desire and will be available to respond to appropriate questions.

Neither our Bylaws nor other governing documents or law require stockholder ratification of the selection of Ernst & Young LLP as our independent auditors. However, the Audit Committee is submitting the selection of Ernst & Young LLP to our stockholders for ratification as a matter of good corporate practice. If our stockholders fail to ratify the selection, the Audit Committee will reconsider whether or not to retain Ernst & Young LLP. Even if the selection is ratified, the Audit Committee in its discretion may direct the appointment of different independent auditors at any time during the year if they determine that such a change would be in the best interests of Metabasis and our stockholders.

To be approved, the ratification of the selection of Ernst & Young LLP as our independent auditors must receive a "For" vote from the majority of shares present and entitled to vote either in person or by proxy. Abstentions will be counted toward the tabulation of votes cast on proposals presented to the stockholders and will have the same effect as negative votes. Broker non-votes will be counted towards a quorum, but will not be counted for any purpose in determining whether this matter has been approved.

#### Principal Accountant Fees and Services

The following table provides information regarding the fees billed to us by Ernst & Young LLP for the fiscal years ended December 31, 2004 and 2003. All fees described below were approved by the Audit Committee.

	Fiscal Year Ended December 31,	
	2004	2003
Audit Fees(1) .....	\$494,089	\$124,043
Audit-related Fees(2) .....	—	8,882
Tax Fees(3) .....	15,726	10,355
All Other Fees .....	—	—
Total Fees .....	\$509,815	\$143,280

- (1) Represents fees for services rendered for the audit and/or reviews of our financial statements. Also includes fees for services associated with SEC registration statements, periodic reports and other documents filed with the SEC or other documents issued in connection with securities offerings (e.g., comfort letters and consents), and assistance in responding to SEC comment letters.
- (2) Represents fees for consultation as to the accounting or disclosure treatment of transactions or events and/or the actual or potential impact of final or proposed rules, standards or interpretations by the SEC, Financial Accounting Standards Board, or other regulatory or standard-setting bodies, as well as assistance with implementation of the requirements of SEC rules or listing standards promulgated pursuant to the Sarbanes-Oxley Act of 2002.
- (3) Represents fees for preparation of federal, state and local income and franchise tax returns and related schedules and calculations, as well as general consultation regarding federal and state income tax matters, employment tax matters and sales and use tax matters.

**Pre-Approval Policies and Procedures**

The Audit Committee has adopted an Audit and Non-Audit Services Pre-Approval Policy, which sets forth the procedures and the conditions pursuant to which services proposed to be performed by our independent auditors are, or may be, pre-approved. A copy of the Audit and Non-Audit Services Pre-Approval Policy is attached as Appendix B to this proxy statement.

The Audit Committee has determined that the rendering of the services other than audit services by Ernst & Young LLP is compatible with maintaining Ernst & Young LLP's independence.

**THE BOARD OF DIRECTORS RECOMMENDS A VOTE *FOR* THE RATIFICATION OF THE SELECTION OF ERNST & YOUNG LLP AS OUR INDEPENDENT AUDITORS FOR THE FISCAL YEAR ENDING DECEMBER 31, 2005.**

## SECURITY OWNERSHIP OF CERTAIN BENEFICIAL OWNERS AND MANAGEMENT

The following table provides information regarding the beneficial ownership of our common stock as of March 1, 2005 by: (i) each of our directors, (ii) each of our executive officers, (iii) all of our directors and executive officers as a group and (iv) each person, or group of affiliated persons, known by us to beneficially own more than five percent of our common stock. The table is based upon information supplied by our officers, directors and principal stockholders and a review of Schedules 13D and 13G, if any, filed with the SEC. Unless otherwise indicated in the footnotes to the table and subject to community property laws where applicable, we believe that each of the stockholders named in the table has sole voting and investment power with respect to the shares indicated as beneficially owned.

Applicable percentages are based on 18,180,482 shares outstanding on March 1, 2005, adjusted as required by rules promulgated by the SEC. These rules generally attribute beneficial ownership of securities to persons who possess sole or shared voting power or investment power with respect to those securities. In addition, the rules include shares of common stock issuable pursuant to the exercise of stock options or warrants that are either immediately exercisable or exercisable on April 30, 2005, which is 60 days after March 1, 2005. These shares are deemed to be outstanding and beneficially owned by the person holding those options or warrants for the purpose of computing the percentage ownership of that person, but they are not treated as outstanding for the purpose of computing the percentage ownership of any other person.

<u>Name and Address of Beneficial Owner(1)</u>	<u>Number of Shares Beneficially Owned</u>	<u>Percentage of Shares Beneficially Owned</u>
MPM Capital L.P. and its affiliates(2) ..... 111 Huntington Avenue, 31 <sup>st</sup> Floor Boston, Massachusetts 02199	4,475,398	23.7%
InterWest Management Partners VII, LLC and its affiliates(3) ..... 2710 Sand Hill Road, Second Floor Menlo Park, California 94025	2,618,680	14.1
Sicor Inc. .... 19 Hughes Irvine, California 92618	2,114,253	11.6
Sprout Capital IX, L.P. and its affiliates(4) ..... 3000 Sand Hill Road Building 3, Suite 170 Menlo Park, California 94025	1,894,624	10.3
Maverick Capital, Ltd. and its affiliates(5) ..... 300 Crescent Court, 18 <sup>th</sup> Floor Dallas, Texas 75201	1,291,388	7.1
Wellington Management Company, LLP ..... 75 State Street Boston, Massachusetts 02109	1,000,000	5.5
Paul K. Laikind(6) .....	776,072	4.3
Mark D. Erion(7) .....	702,628	3.9
John W. Beck(8) .....	277,709	1.5
Edgardo Baracchini(9) .....	135,503	*
Daniel D. Burgess(10) .....	7,634	*
Luke B. Evin(2) .....	4,475,398	23.7
Heinz W. Gschwend(11) .....	37,094	*
David F. Hale(12) .....	60,741	*
Arnold L. Oronsky, Ph.D.(3) .....	2,618,680	14.1
William R. Rohn(13) .....	3,328	*
All directors and executive officers as a group (10 persons)(14) .....	9,094,787	46.6

\* Less than one percent.

- (1) Except as otherwise noted above, the address for each person or entity listed in the table is c/o Metabasis Therapeutics, Inc., 9390 Towne Centre Drive, Building 300, San Diego, California 92121.
- (2) Includes 282,146 shares held by MPM BioVentures II, L.P., 2,557,075 shares held by MPM BioVentures II-QP, L.P., 900,225 shares held by MPM BioVentures GmbH & Co. Parallel-Beteiligungs KG and 58,873 shares held by MPM Asset Management Investors 2000 B LLC. Also includes 668,759 shares MPM BioVentures II, L.P., MPM BioVentures II-QP, L.P., MPM BioVentures GmbH & Co. Parallel-Beteiligungs KG and MPM Asset Management Investors 2000 B LLC have the right to acquire from us within 60 days of March 1, 2005 pursuant to the exercise of warrants. Also includes 8,320 shares that Dr. Evinin has the right to acquire from us within 60 days of March 1, 2005 pursuant to the exercise of stock options. MPM Capital L.P. is a direct or indirect parent and/or control person of MPM Asset Management II LLC, funds managed or advised by it (including MPM BioVentures II, L.P., MPM BioVentures II-QP, L.P., MPM BioVentures GmbH & Co. Parallel-Beteiligungs KG, and MPM Asset Management Investors 2000 B LLC) and the general partners of such funds, and may be deemed to beneficially hold the securities owned by such entities. Dr. Evinin may be deemed to be a control person of MPM Capital L.P. as a result of his interest in Medical Portfolio Management LLC, the general partner of MPM Capital L.P. Dr. Evinin disclaims beneficial ownership of these shares except to the extent of his pecuniary interest in these entities.
- (3) Includes 2,103,329 shares held by InterWest Partners VII, L.P. and 100,723 shares held by InterWest Investors VII, L.P. Also includes 406,308 shares InterWest Partners VII, L.P. and InterWest Investors VII, L.P. have the right to acquire from us within 60 days of March 1, 2005 pursuant to the exercise of warrants. Also includes 8,320 shares that Dr. Oronsky has the right to acquire from us within 60 days of March 1, 2005 pursuant to the exercise of stock options. Dr. Oronsky is a managing director of InterWest Management Partners VII, LLC, the general partner of InterWest Partners VII, L.P. and InterWest Investors VII, L.P. Dr. Oronsky disclaims beneficial ownership of these shares except to the extent of his pecuniary interest in these entities.
- (4) Includes 1,538,153 shares held by Sprout Capital IX, L.P., 18,578 shares held by DLJ Capital Corp., 82,941 shares held by Sprout IX Plan Investors, L.P. and 6,061 shares held by Sprout Entrepreneurs Fund, L.P. Also includes 248,891 shares Sprout Capital IX, L.P., DLJ Capital Corp., Sprout IX Plan Investors, L.P. and Sprout Entrepreneurs Fund, L.P. have the right to acquire from us within 60 days of March 1, 2005 pursuant to the exercise of warrants. Kathleen LaPorte is the managing director of DLJ Capital Corp., the managing general partner of Sprout Capital IX, L.P. and general partner of Sprout Entrepreneurs Fund, L.P. DLJ LBO Plans Management Corporation II is the general partner of Sprout IX Plan Investors, L.P. and is an affiliate of DLJ Capital Corp. Ms. LaPorte disclaims beneficial ownership of these shares except to the extent of her pecuniary interest in these entities.
- (5) Includes 739,984 shares held by Maverick Fund, L.D.C., 338,902 shares held by Maverick Fund USA, Ltd., 207,502 shares held by Maverick Fund II, Ltd., 1,000 shares held by Maverick Neutral Fund, Ltd., 2,000 shares held by Maverick Neutral Leverage Fund, Ltd. and 2,000 shares held by Maverick Long Fund, Ltd. Lee S. Ainslie III exercises sole voting and dispositive power over the shares held by Maverick Fund, L.D.C., Maverick Fund USA, Ltd., Maverick Fund II, Ltd., Maverick Neutral Fund, Ltd., Maverick Neutral Leverage Fund, Ltd. and Maverick Long Fund, Ltd. Mr. Ainslie disclaims beneficial ownership of these shares except to the extent of his pecuniary interest in these entities.
- (6) Includes 125,014 unvested shares which are subject to a right of repurchase in our favor as of March 1, 2005. Also includes 61,437 shares that Dr. Laikind has the right to acquire from us within 60 days of March 1, 2005 pursuant to the exercise of stock options, 38,399 of which would be initially unvested and subject to a right of repurchase by us as of April 30, 2005 that would lapse over the vesting schedule.
- (7) Includes 115,754 unvested shares which are held by the Erion Family Trust and are subject to a right of repurchase in our favor as of March 1, 2005. Also includes an additional 517,639 shares held by the Erion Family Trust, 49,382 shares held by each of the Mark Erion 2002 Grantor Retained Annuity Trust and the Sonja Erion 2002 Grantor Retained Annuity Trust, and 15,089 shares held by each of the Derek Mark Erion 2003 Irrevocable Trust, the Renske Marie Erion 2003 Irrevocable Trust and the Karel Arnt Erion 2003 Irrevocable Trust. Also includes 40,958 shares that Dr. Erion has the right to acquire from us within 60 days of March 1, 2005 pursuant to the exercise of stock options, 25,599 of which would be initially unvested and subject to a right of repurchase by us as of April 30, 2005 that would lapse over the vesting schedule.

- (8) Includes 61,933 unvested shares which are subject to a right of repurchase in our favor as of March 1, 2005. Also includes 12,345 shares held by each of Katherine M. Dye, Ttee. Katerina F. Beck 2002 Irrev. Trust Dtd. 11/8/02, Katherine M. Dye, Ttee. Joseph C. Beck 2002 Irrev. Trust Dtd. 11/8/02 and Katherine M. Dye, Ttee. Rachael M. Beck 2002 Irrev. Trust. Dtd. 11/8/02.
- (9) Includes 33,890 shares held by the Edgardo and Suzanne Baracchini Living Trust dtd 4/22/98. Also includes 101,613 shares that Dr. Baracchini has the right to acquire from us within 60 days of March 1, 2005 pursuant to the exercise of stock options, 70,539 of which would be initially unvested and subject to a right of repurchase by us as of April 30, 2005 that would lapse over the vesting schedule.
- (10) Represents 12,165 shares that Mr. Burgess has the right to acquire from us within 60 days of March 1, 2005 pursuant to the exercise of stock options, 4,801 of which would be initially unvested and subject to a right of repurchase by us as of April 30, 2005 that would lapse over the vesting schedule.
- (11) Includes 27,458 shares held by the H.W. Gschwend & C.T. Healy Revocable Trust, of which Dr. Gschwend is a co-trustee. Also includes 9,636 shares that Dr. Gschwend has the right to acquire from us within 60 days of March 1, 2005 pursuant to the exercise of stock options.
- (12) Includes 47,226 shares held by the Hale Family Trust dated February 10, 1986. Also includes 3,111 shares the Hale Family Trust has the right to acquire from us within 60 days of March 1, 2005 pursuant to the exercise of warrants. Also includes 10,404 shares that Mr. Hale has the right to acquire from us within 60 days of March 1, 2005 pursuant to the exercise of stock options.
- (13) Represents 3,328 shares that Mr. Rohn has the right to acquire from us within 60 days of March 1, 2005 pursuant to the exercise of stock options.
- (14) Includes 302,701 unvested shares which are subject to a right of repurchase in our favor as of March 1, 2005, 256,181 shares pursuant to the exercise of stock options within 60 days of March 1, 2005, 139,338 of which would be initially unvested and subject to a right of repurchase by us as of April 30, 2005 that would lapse over the vesting schedule, and 1,078,178 shares pursuant to the exercise of warrants within 60 days of March 1, 2005.

#### **SECTION 16(A) BENEFICIAL OWNERSHIP REPORTING COMPLIANCE**

Section 16(a) of the Securities Exchange Act of 1934 requires our directors and executive officers, and persons who own more than ten percent of a registered class of our equity securities, to file with the SEC initial reports of ownership and reports of changes in ownership of our common stock and other equity securities. Officers, directors and greater than ten percent stockholders are required by SEC regulation to furnish us with copies of all Section 16(a) forms they file.

To our knowledge, based solely on a review of the copies of such reports furnished to us and written representations that no other reports were required, during the fiscal year ended December 31, 2004, all Section 16(a) filing requirements applicable to our officers, directors and greater than ten percent beneficial owners were complied with, except that one report of changes in ownership was inadvertently filed late by each of Mr. Burgess and Dr. Oronsky.

#### **COMPENSATION OF DIRECTORS**

We provide each of our non-employee directors cash compensation in the form of an annual retainer of \$15,000, plus \$8,000 for the chair of the Audit Committee, \$5,000 for the other members of the Audit Committee and \$2,500 for all other committee members. We also reimburse our non-employee directors for their reasonable expenses incurred in attending meetings of our Board of Directors and committees of the Board.

Each of our non-employee directors also receives stock option grants under our 2004 Non-Employee Directors' Stock Option Plan, or the Directors' Plan. Only our non-employee directors or an affiliate of such directors (as defined in the Internal Revenue Code) are eligible to receive options under the Directors' Plan. Options granted under the Directors' Plan are intended by us not to qualify as incentive stock options under the Internal Revenue Code.

Option grants under the Directors' Plan are non-discretionary. Pursuant to the terms of the Directors' Plan, upon the completion of our initial public offering in June 2004, each non-employee director was automatically granted an option to purchase 20,000 shares of our common stock, less the number of shares of common stock, if any, subject to an option or options granted to the director within the six month period prior to the completion of the offering, as adjusted for the reverse stock split of our common stock that occurred in May 2004.

Any person who becomes a non-employee director after the completion of our initial public offering will automatically receive an option to purchase 20,000 shares of common stock upon his or her election. In addition, any person who is a non-employee director on the date of each annual meeting of our stockholders will be automatically granted, on the annual meeting date, an option to purchase 10,000 shares of common stock. However, the size of this annual grant made to a non-employee director who has served for less than 12 months at the time of the annual meeting will be reduced by 25% for each full quarter prior to the date of grant during which such person did not serve as a non-employee director. No other stock options may be granted at any time under the Directors' Plan.

The exercise price of stock options granted under the Directors' Plan is equal to 100% of the fair market value of the common stock on the date of grant. Initial grants (i.e., those made on the completion of our initial public offering or upon a non-employee director's election to our Board of Directors after our initial public offering) vest at the rate of  $\frac{1}{24}$ <sup>th</sup> each month after the date of grant, and annual grants vest at the rate of  $\frac{1}{12}$ <sup>th</sup> each month after the date of grant. In general, the term of stock options granted under the Directors' Plan may not exceed ten years.

Unless the terms of an optionholder's stock option agreement provide for earlier termination, if an optionholder's service relationship with us, or any affiliate of ours, ceases due to disability or death, the optionholder, or his or her beneficiary, may exercise any vested options up to 12 months, or 18 months in the event of death, after the date such service relationship ends. If an optionholder's service relationship with us, or any affiliate of ours, ceases without cause for any reason other than disability or death, the optionholder may exercise any vested options up to three months from cessation of service, unless the terms of the stock option agreement provide for earlier or later termination.

Acceptable consideration for the purchase of common stock issued under the Directors' Plan may include cash or check, common stock previously owned by the optionholder or a program developed under Regulation T as promulgated by the Federal Reserve Board. Generally, an optionholder may not transfer a stock option other than by will or the laws of descent and distribution. An optionholder may transfer an option with our written consent provided a Form S-8 registration statement is available for the exercise of the option and the subsequent resale of the shares. However, an optionholder may designate a beneficiary who may exercise the option following the optionholder's death.

In the event of certain corporate transactions, any or all outstanding options under the Directors' Plan may be assumed or substituted for by any surviving entity. If the surviving entity elects not to assume or substitute for all such options, the vesting provisions of the options not assumed or substituted for and held by participants whose continuous service has not terminated will be accelerated and such options will be terminated if not exercised prior to the effective date of the corporate transaction. In the event of a change in our control, the vesting provisions of all outstanding options under the Directors' Plan will be accelerated and such options will be terminated if not exercised prior to 12 months after the effective date of the change in our control.

Under the Directors' Plan, during the fiscal year ended December 31, 2004, we made initial grants to purchase 90,784 shares at an exercise price of \$6.50 per share upon the completion of our initial public offering to each of our non-employee directors other than Mr. Rohn, and we made an initial grant to purchase 20,000 shares at an exercise price of \$7.15 per share to Mr. Rohn upon his election to our Board

of Directors in December 2004. As of March 1, 2005, no stock options had been exercised under the Directors' Plan.

In addition, Heinz W. Gschwend, as a member of our scientific advisory board, is entitled to a reasonable daily rate for attendance at authorized scientific advisory board meetings, as well as reimbursement for reasonable expenses incurred in attending meetings. As our scientific advisory board did not meet during the fiscal year ended December 31, 2004, Mr. Gschwend did not receive any such fees in the last fiscal year.

## COMPENSATION OF EXECUTIVE OFFICERS

### Summary of Compensation

The following table provides information regarding the compensation earned during the fiscal years ended December 31, 2004 and 2003 by our Chief Executive Officer and each of our other executive officers whose combined salary and bonus exceeded \$100,000 for that fiscal year. We refer to these officers in this proxy statement as the "Named Executive Officers".

Summary Compensation Table(1)

Name and Principal Position	Year(2)	Annual Compensation			Long-Term Compensation		All Other Compensation(4)
		Salary (\$)	Bonus (\$)	Other Annual Compensation (\$)	Restricted Stock Awards(3) (\$)	Securities Underlying Options (#)	
Paul K. Laikind . . . . .	2004	\$326,539	\$90,668	—	—	—	\$49,770
Chairman of the Board, President, Chief Executive Officer and Secretary	2003	297,115	87,150	—	\$ 32,461	61,437	78,001
Mark D. Erion . . . . .	2004	272,115	64,948	—	—	—	58,474
Executive Vice President of Research and Development	2003	247,808	63,488	—	289,314	40,958	75,781
John W. Beck . . . . .	2004	208,269	50,471	—	—	—	26,305
Vice President of Finance, Chief Financial Officer and Treasurer	2003	192,923	48,818	—	109,297	27,305	32,843
Edgardo Baracchini . . . . .	2004	218,269	51,934	—	—	37,181	—
Vice President of Business Development	2003	205,000	50,215	—	—	27,995	—

- (1) In accordance with the rules of the SEC, the compensation described in this table does not include various perquisites and other benefits received by a Named Executive Officer which do not exceed the lesser of \$50,000 or 10% of that officer's salary and bonus disclosed in this table.
- (2) In accordance with the rules of the SEC, no amounts are shown for 2002 as we completed our initial public offering during 2004.
- (3) Represents 214,307, 198,432 and 74,963 shares of previously vested common stock held by Drs. Laikind and Erion and Mr. Beck, respectively, tendered to us on June 30, 2003 and subjected to a new monthly vesting schedule over a four-year period beginning on that date. These shares were tendered in part as repayment for outstanding principal and interest on loans we made to Drs. Laikind and Erion and Mr. Beck in connection with their purchase of our common stock in June 1999, the outstanding amount of which at June 30, 2003 was equal to \$229,374, \$206,438 and \$77,988, respectively. Drs. Laikind and Erion and Mr. Beck continued to hold these shares at December 31, 2004, on which date their value was equal to \$1,553,726, \$1,438,632 and \$543,482, respectively, based on the closing price of our common stock for that day as reported on the Nasdaq (\$7.25). We do not currently intend to pay dividends on these shares.

- (4) For 2003, represents \$28,620, \$33,625 and \$15,604 reimbursed by us for income tax payments incurred by Drs. Laikind and Erion and Mr. Beck, respectively, plus \$49,381, \$42,156 and \$17,239, respectively, in income tax payments made by us on their behalf in connection with the transaction described in footnote (3) above and which were not otherwise satisfied by us through the application of the value of the shares tendered to us. For 2004, represents \$49,770, \$58,474 and \$26,305 in income tax payments made by us on behalf of Drs. Laikind and Erion and Mr. Beck, respectively, also in connection with the transaction described in footnote (3) above and which were not otherwise satisfied by us through the application of the value of the shares tendered to us.

### **Stock Option Grants And Exercises**

We grant stock options to our executive officers under our Amended and Restated 2001 Equity Incentive Plan, or the Incentive Plan. As of March 1, 2005, options to purchase a total of 960,165 shares were outstanding under the Incentive Plan, and a total of 1,479,610 shares remained available for grant under the Incentive Plan.

All stock options granted to our executive officers are incentive stock options, to the extent permissible under the Internal Revenue Code. Generally, 25% of the shares subject to options vest one year from the date of hire and the remainder of the shares vest in equal monthly installments over the 36 months thereafter, subject to cessation of vesting upon the termination of the optionholder's continued service to us and to acceleration of vesting pursuant to the stock restriction agreements described in "Employment, Severance and Change of Control Agreements." Options expire ten years from the date of grant.

The exercise price per share of each option granted to our executive officers was equal to the fair market value of our common stock on the date of the grant. Prior to the completion of our initial public offering in June 2004, our Board of Directors determined the fair market value of our common stock after considering many factors, including:

- the rate of progress and cost of our clinical trials and other research and development activities,
- the terms and timing of any collaborative, licensing and other arrangements that we may establish,
- the fact that our options involved illiquid securities in a non-public company,
- prices of preferred stock issued by us to outside investors in arm's-length transactions,
- the rights, preferences and privileges of our preferred stock over our common stock, and
- the likelihood that our common stock would become liquid through an initial public offering, an acquisition of us or another event.

Following the completion of our initial public offering, pursuant to the Incentive Plan, the fair market value of our common stock on a given date is deemed to be equal to the closing sales price for such stock as reported on the Nasdaq on the last market trading day prior to such date.

The following table provides information regarding grants of options to purchase shares of our common stock to the Named Executive Officers in the fiscal year ended December 31, 2004.

Name	Individual Grants				Potential Realizable Value at Assumed Annual Rates of Stock Price Appreciation for Option Term(2)	
	Number of Securities Underlying Options Granted (#)	% of Total Options Granted to Employees in Fiscal Year(1)	Exercise Or Base Price (\$/Sh)	Expiration Date	5% (\$)	10% (\$)
Paul K. Laikind . . . . .	—	—	—	—	—	—
Mark D. Erion . . . . .	—	—	—	—	—	—
John W. Beck . . . . .	—	—	—	—	—	—
Edgardo Baracchini . . . . .	9,876	3%	\$1.46	03/03/2014	\$ 98,190	\$164,892
	27,305	8	1.46	05/18/2014	271,473	455,890

- (1) Based on 333,951 options granted during the fiscal year ended December 31, 2004 under the Incentive Plan, including grants to executive officers.
- (2) Potential realizable values are computed by (a) multiplying the number of shares of common stock subject to a given option by our initial public offering price of \$7.00 per share, (b) assuming that the aggregate stock value derived from that calculation compounds at the annual 5% or 10% rate shown in the table for the entire ten-year term of the option and (c) subtracting from that result the aggregate option exercise price. The 5% and 10% assumed annual rates of stock price appreciation are mandated by the rules of the SEC and do not represent our estimate or projection of future common stock prices.

#### Aggregate Option Exercises in Last Fiscal Year and Fiscal Year-End Option Values

The following table provides information regarding the number of shares of common stock subject to exercisable and unexercisable stock options held as of December 31, 2004 by each of the Named Executive Officers. All options listed in the table permit early exercise of unvested shares, in which case all unvested shares are subject to repurchase by us.

Name	Shares Acquired on Exercise (#)	Value Realized \$(1)	Number of Securities Underlying Unexercised Options at Fiscal Year-End		Value of Unexercised In-the-Money Options at Fiscal Year-End(2)	
			Exercisable (#)	Unexercisable (#)	Exercisable (\$)	Unexercisable (\$)
Paul K. Laikind . . . . .	—	—	61,437	—	\$355,720	—
Mark D. Erion . . . . .	—	—	40,958	—	237,147	—
John W. Beck . . . . .	27,305	\$151,270	—	—	—	—
Edgardo Baracchini . . . . .	33,521	185,706	101,613	—	588,339	—

- (1) The value realized of shares acquired on exercise is equal to the excess of the initial public offering price of \$7.00 per share over the exercise price for the option, multiplied by the number of shares subject to the option, without taking into account any taxes that may be payable in connection with the transaction. Mr. Beck and Dr. Baracchini exercised the options listed prior to our initial public offering.
- (2) The value of an unexercised in-the-money option as of December 31, 2004 is equal to the excess of the closing price of our common stock for that day as reported on the Nasdaq (\$7.25) over the exercise price for the option, multiplied by the number of shares subject to the option, without taking into account any taxes that may be payable in connection with the transaction.

## **Employment, Severance and Change of Control Agreements**

### *Offer Letters*

We have entered into offer letters with Mr. Beck and Dr. Baracchini, setting forth their respective base salary, bonus eligibility and other employment benefits. We have not entered into offer letters with Drs. Laikind or Erion. Each Named Executive Officer's employment is on an "at-will" basis and can be terminated by us or the officer at any time, for any reason and with or without notice, subject where applicable to the stock restriction agreements and severance agreements described below.

### *Proprietary Information and Inventions Agreements*

Each Named Executive Officer has also entered into a standard form agreement with respect to proprietary information and inventions. Among other things, this agreement obligates the officer to refrain from disclosing any of our confidential information received during the course of employment and, with some exceptions, to assign to us any inventions conceived or developed during the course of employment.

### *Stock Restriction Agreements*

We have entered into stock restriction agreements with Mr. Beck and Drs. Erion and Laikind, under which we have an option to repurchase shares of common stock held by each officer within 60 days following the termination of his respective employment. Our repurchase option lapses in equal monthly installments over the 48 months following the date of each officer's stock restriction agreement, as long as he continues to be employed by us. However, if we terminate the officer without cause or he terminates his employment for good reason, our repurchase option lapses in its entirety. As of December 31, 2004, our repurchase option covered 46,853, 124,022 and 133,944 shares held by Mr. Beck and Drs. Erion and Laikind, respectively.

### *Severance Agreements*

We have entered into severance agreements with each of the Named Executive Officers. These agreements provide that each officer is generally entitled to his base salary, plus the average of his annual bonuses for the last three completed calendar years, for a continuation period of nine months following the termination of his employment if, during the 12-month period following a change in our control, the officer terminates his employment for good reason, or the officer's employment is terminated without cause or pursuant to a restructuring or reduction in force. The continuation period is extended to 12 months if the officer is not employed in a comparable position at the end of the nine-month continuation period. A termination entitling an officer to the cash severance described above also causes immediate vesting of any unvested stock options or shares of restricted stock that are not covered by the officer's stock restriction agreement, if applicable. Following such a termination, the officer is entitled to convert his long-term disability and group life insurance policies to individual policies and to continue his group health insurance coverage, and we will pay all related premiums during the continuation period. In addition, the officer is entitled to reasonable outplacement services at our expense.

## **Pension and Long-Term Incentive Plans**

We have no pension plans or long-term incentive plans.

### Equity Compensation Plan Information

The following table provides certain information as of December 31, 2004, with respect to all of our equity compensation plans in effect on that date.

	Number of securities to be issued upon exercise of outstanding options, warrants and rights (a)	Weighted-average exercise price of outstanding options, warrants and rights (b)	Number of securities remaining available for issuance under equity compensation plans (excluding securities reflected in column (a)) (c)
Equity compensation plans approved by stockholders(1) . . .	2,454,683	\$5.13	1,525,591
Equity compensation plans not approved by stockholders(2) . . .	<u>—</u>	<u>—</u>	<u>—</u>
Total . . . . .	<u>2,454,683</u>	<u>\$5.13</u>	<u>1,525,591</u>

(1) Includes the Incentive Plan, the Directors' Stock Plan and our 2004 Employee Stock Purchase Plan. 500,000 shares under column (c) are attributable to our 2004 Employee Stock Purchase Plan.

(2) As of December 31, 2004, we did not have any equity compensation plans that were not approved by our stockholders.

**REPORT OF THE COMPENSATION COMMITTEE OF THE BOARD OF DIRECTORS  
ON EXECUTIVE COMPENSATION**

*The material in this report is not "soliciting material," is not deemed "filed" with the Securities and Exchange Commission, and is not to be incorporated by reference into any filing of Metabasis under the Securities Act of 1933, as amended, or the Securities Exchange Act of 1934, as amended.*

**Introduction**

The primary purpose of the Compensation Committee is to act on behalf of our Board of Directors in overseeing our compensation policies, plans and programs and determining the compensation to be paid to our executive officers. The Compensation Committee's functions are more fully described in its charter, which is available on our website at <http://www.mbasis.com>.

The purpose of this report is to summarize the Compensation Committee's philosophy regarding executive compensation, explain the elements of our executive compensation structure, and describe the basis upon which the Compensation Committee determined the compensation of our Chief Executive Officer for the fiscal year ended December 31, 2004.

**Compensation Philosophy**

The Compensation Committee believes that a well-designed compensation program for our executive officers should:

- align the goals of our executive officers with the goals of our stockholders by creating and enhancing stockholder value through the accomplishment of corporate performance goals and by providing executive officers with long-term incentives through equity ownership,
- recognize individual initiative, effort and achievement,
- provide total compensation that enables us to compete with companies in the biopharmaceutical and biotechnology industries, in order to attract and retain high-caliber candidates on a long-term basis, and
- align compensation with our short-term and long-term corporate objectives and strategy, focusing executive officer behavior on the fulfillment of those objectives.

**Elements of Executive Compensation**

Currently, our compensation structure for executive officers consists of a combination of base salary, performance bonuses and long-term incentives (typically, stock option awards). Executive officers are also entitled to participate in benefit plans generally available to employees.

*Base Salary.* As a general matter, we establish an initial base salary for each executive officer through negotiation at the time the executive officer is hired, taking into account the executive officer's qualifications, experience, prior base salary and independent compensation survey data for comparable companies. We make periodic adjustments to each executive officer's base salary based upon an evaluation of independent compensation survey data for comparable companies as well as the executive officer's individual performance against pre-established objectives. The Compensation Committee utilizes compensation survey data that includes a cross-industry subset of companies generally considered to be comparable to our company. The survey data includes the Biotech Employee Development Coalition (BEDC) Survey and the Radford Survey. The BEDC Survey includes 75 biotechnology companies local to us and the Radford Survey includes over 500 national biotech and pharmaceutical companies. Although the Compensation Committee does not use a specific formula to set pay in relation to this market data, it

generally targets executive officer base salaries at the median of the salary ranges identified in the compensation survey data.

*Performance Bonuses.* We may award performance bonuses to motivate and reward executive officers based upon their achievement of individual performance goals, as well as our achievement of corporate performance goals. Individual performance goals vary with an executive officer's responsibilities and are based on individual objectives. Corporate performance goals are set annually and reflect high priority company-wide objectives. The Compensation Committee generally targets bonus amounts at the median of the ranges identified in the compensation survey data referred to above. We believe using corporate performance goals to determine performance bonuses establishes a direct link between executive officer compensation and our financial performance.

*Long-Term Incentives.* Our long-term incentives are primarily in the form of stock option grants. The objective of these grants is to emphasize long-term performance and the creation of stockholder value. As the exercise price per share of options we grant to our executive officers is generally equal to the fair market value of our common stock on the date of grant, the options will only produce value if the price of our stock appreciates, thereby directly linking the interests of our executive officers with those of stockholders. In determining the amount of stock options granted to an executive officer, the Compensation Committee evaluates not only the independent compensation survey data for comparable companies referred to above and individual performance against pre-established objectives, but also the size and terms of equity awards previously made to the executive officer. The Compensation Committee generally targets executive officer stock option grants that maintain each executive's overall stock option position with us at the median of the ranges identified in the compensation survey data referred to above.

#### **Chief Executive Officer Compensation**

The base salary of Paul K. Laikind, Ph.D., our Chief Executive Officer, was \$330,000 for the fiscal year ended December 31, 2004, an increase of \$30,000 from his base salary for the prior year. Dr. Laikind was granted a performance bonus of \$90,668 for the fiscal year ended December 31, 2004. Dr. Laikind did not receive any stock options during the fiscal year ended December 31, 2004.

The Compensation Committee followed the approach described above in establishing Dr. Laikind's compensation for 2004 with a significant portion of his compensation depending on the achievement of financial and non-financial performance criteria. In determining Dr. Laikind's performance bonus for the fiscal year ended December 31, 2004, the Compensation Committee recognized Dr. Laikind's efforts in helping us achieve the following corporate objectives during 2004:

- the completion of our initial public offering,
- the completion of two studies with our partner Valeant Pharmaceuticals International that evaluated the action of pradefovir in patients infected with hepatitis B and demonstrated a statistically and clinically significant reduction of viral titer,
- the initiation of and completion of enrollment in a Phase 2B study of pradefovir designed to select the optimum dosing regimen for potential study of the drug in pivotal Phase 3 trials,
- the continued studies of MB07133 in patients with primary liver cancer designed to identify the maximum tolerated dose,
- completion of a 28-day Phase 2A study of CS-917 that provided evidence that CS-917 is capable of significantly reducing blood glucose levels in patients with type 2 diabetes,
- the initiation of a dose ranging Phase 2B study of CS-917 in patients with type 2 diabetes,

- the initiation of collaborative work with Merck & Co., Inc. to identify new treatments for hepatitis C viral infection through the application of our proprietary liver targeting technology to certain Merck product candidates,
- the publishing of key reports on the HepDirect technology in prestigious journals,
- the presentation of clinical data on pradefovir at the 55th Annual Meeting of the American Society for the Study of Liver Diseases (AASLD), and
- the enhancement of the capabilities of our board and management team.

#### **Section 162(m) Compliance**

Section 162(m) of the Internal Revenue Code generally prohibits us from deducting any compensation over \$1 million per taxable year paid to any of the Named Executive Officers unless such compensation is treated as “performance-based compensation” within the meaning of the Internal Revenue Code. As the cash compensation paid by us to the Named Executive Officers is expected to be below \$1 million and the Compensation Committee believes that stock options granted under the Incentive Plan to the Named Executive Officers meet the requirements for treatment as performance-based compensation, the Compensation Committee believes that Section 162(m) will not affect the tax deductions available to the Company with respect to the compensation of its executives. In determining the form and amount of compensation for Named Executive Officers, the Compensation Committee will continue to consider all elements of the cost of such compensation, including the potential impact of Section 162(m).

#### **Compensation Committee**

Arnold L. Oronsky, Ph.D., Chairman  
David F. Hale  
Heinz W. Gschwend, Ph.D.

## REPORT OF THE AUDIT COMMITTEE OF THE BOARD OF DIRECTORS

*The material in this report is not "soliciting material," is not deemed "filed" with the Securities and Exchange Commission, and is not to be incorporated by reference into any filing of Metabasis under the Securities Act of 1933, as amended, or the Securities Exchange Act of 1934, as amended.*

The primary purpose of the Audit Committee is to oversee our financial reporting processes on behalf of our Board of Directors. The Audit Committee's functions are more fully described in its charter, which is available on our website at <http://www.mbasis.com> and is attached as Appendix A to this proxy statement. Management has the primary responsibility for our financial statements and reporting processes, including our systems of internal controls. In fulfilling its oversight responsibilities, the Audit Committee reviewed and discussed with management our audited financial statements as of and for the fiscal year ended December 31, 2004.

The Audit Committee reviewed with Ernst & Young LLP such matters as are required to be discussed with the Audit Committee under generally accepted auditing standards, including the matters required to be discussed by Statement on Auditing Standards No. 61. In addition, the Audit Committee discussed with Ernst & Young LLP their independence, and received from Ernst & Young LLP the written disclosures and the letter required by Independence Standards Board Standard No. 1. Finally, the Audit Committee discussed with Ernst & Young LLP, with and without management present, the scope and results of Ernst & Young LLP's audit of such financial statements.

Based on these reviews and discussions, the Audit Committee has recommended to our Board of Directors that such audited financial statements be included in our Annual Report on Form 10-K for the year ended December 31, 2004 for filing with the Securities and Exchange Commission. The Audit Committee also has engaged Ernst & Young LLP as our independent auditors for the fiscal year ending December 31, 2005 and is seeking ratification of such selection by the stockholders.

### **Audit Committee**

Daniel D. Burgess, M.B.A., Chairman  
David F. Hale  
Arnold L. Oronsky, Ph.D.

### COMPENSATION COMMITTEE INTERLOCKS AND INSIDER PARTICIPATION

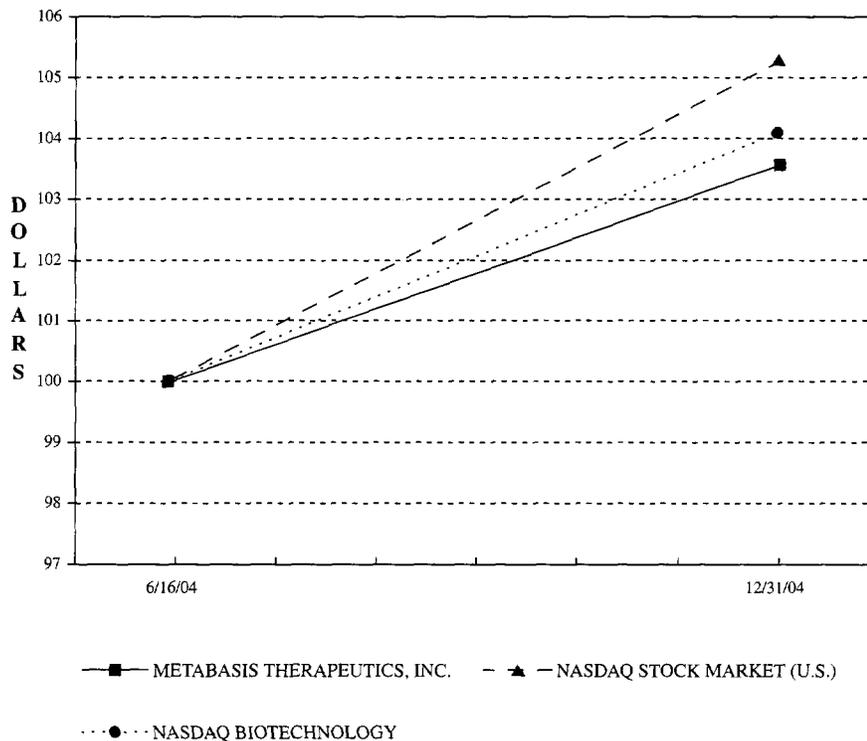
As indicated above, the Compensation Committee consists of Drs. Gschwend and Oronsky and Mr. Hale. No member of the Compensation Committee has ever been an officer or employee of ours. None of our executive officers currently serves, or has served during the last completed fiscal year, on the Compensation Committee or board of directors of any other entity that has one or more executive officers serving as a member of our Board of Directors or Compensation Committee.

### PERFORMANCE MEASUREMENT COMPARISON

*The material in this section is not "soliciting material," is not deemed "filed" with the Securities and Exchange Commission, and is not to be incorporated by reference into any filing of Metabasis under the Securities Act of 1933, as amended, or the Securities Exchange Act of 1934, as amended.*

The following graph shows a comparison of the total cumulative returns of an investment of \$100 in cash (i) on June 16, 2004, the first trading day following our initial public offering, in our common stock, (ii) on May 31, 2004 in the Nasdaq Composite Index, U.S. Companies and (iii) on May 31, 2004 in the Nasdaq Biotechnology Index. The comparisons in the graph are required by the SEC and are not intended to forecast or be indicative of the possible future performance of our common stock. The graph assumes that all dividends have been reinvested (to date, we have not declared any dividends).

### COMPARISON OF 6 MONTH CUMULATIVE TOTAL RETURN AMONG METABASIS THERAPEUTICS, INC., THE NASDAQ STOCK MARKET (U.S.) INDEX AND THE NASDAQ BIOTECHNOLOGY INDEX



## CERTAIN RELATIONSHIPS AND RELATED TRANSACTIONS

In June 2004, we completed an initial closing of our initial public offering involving investments by certain persons, or groups of affiliated persons, known by us to beneficially own more than five percent of our common stock. The following table provides information regarding the number of shares of common stock purchased in our initial public offering by these stockholders.

<u>Participant(1)</u>	<u>Number of Shares Purchased</u>
MPM Capital L.P. and its affiliates .....	357,000
InterWest Management Partners VIII, LLC and its affiliates.....	130,000
Maverick Capital, Ltd. and its affiliates.....	<u>500,000</u>
Totals .....	<u>987,000</u>

- (1) For additional information regarding these stockholders and their equity holdings, please see “Security Ownership of Certain Beneficial Owners and Management.”

During the fiscal year ended December 31, 2004, we granted options to purchase an aggregate of 157,181 shares of common stock to our directors and executive officers, with exercise prices ranging from \$1.46 to \$7.15.

Our bylaws provide that we will indemnify our directors and executive officers, and may indemnify other officers, employees and other agents, to the fullest extent permitted by law. Our bylaws also permit us to secure insurance on behalf of any officer, director, employee or other agent for any liability arising out of his or her actions in connection with their services to us, regardless of whether our amended and restated bylaws permit such indemnification. We have obtained a policy of directors’ and officers’ liability insurance.

We have entered, and intend to continue to enter, into indemnification agreements with our directors and executive officers, in addition to the indemnification provided for in our bylaws. These agreements, among other things, require us to indemnify our directors and executive officers for certain expenses, including attorneys’ fees, judgments, fines and settlement amounts incurred by a director or executive officer in any action or proceeding arising out of their services as one of our directors or executive officers, or any of our subsidiaries or any other company or enterprise to which the person provides services at our request.

## HOUSEHOLDING OF PROXY MATERIALS

The SEC has adopted rules that permit companies and intermediaries (e.g., brokers, banks or other agents) to satisfy the delivery requirements for proxy statements and annual reports with respect to two or more stockholders sharing the same address by delivering a single proxy statement addressed to those stockholders. This process, which is commonly referred to as “householding,” potentially means extra convenience for stockholders and cost savings for companies.

This year, a number of broker, banks or other agents with account holders who are stockholders of Metabasis will be “householding” our proxy materials. A single proxy statement will be delivered to multiple stockholders sharing an address unless contrary instructions have been received from the affected stockholders. Once you have received notice from your broker, bank or other agent that it will be “householding” communications to your address, “householding” will continue until you are notified otherwise or until you revoke your consent. If, at any time, you no longer wish to participate in “householding” and would prefer to receive a separate proxy statement and annual report, please notify your broker, bank or other agent, and direct a written request for the separate proxy statement and annual

report to 9390 Towne Centre Drive, Building 300, San Diego, California 92121, Attn: Secretary, or contact Mr. Beck at (858) 622-3909. Stockholders whose shares are held by their broker, bank or other agent as nominee and who currently receive multiple copies of the proxy statement at their address that would like to request "householding" of their communications should contact their broker, bank or other agent.

#### OTHER MATTERS

Our Board of Directors knows of no other matters that will be presented for consideration at the annual meeting. If any other matters are properly brought before the meeting, it is the intention of the persons named in the accompanying proxy to vote on such matters in accordance with their best judgment.

By Order of the Board of Directors

A handwritten signature in black ink, appearing to be 'P. Laikind', with a horizontal line extending to the right from the end of the signature.

Paul K. Laikind, Ph.D.  
*Chairman of the Board, Chief Executive Officer,  
President and Secretary*

San Diego, California  
April 25, 2005

**A copy of our Annual Report on Form 10-K for the fiscal year ended December 31, 2004 filed with the SEC is available without charge upon written request to: 9390 Towne Centre Drive, Building 300, San Diego, California 92121, Attn: Secretary.**

## APPENDIX A

### CHARTER OF THE AUDIT COMMITTEE OF METABASIS THERAPEUTICS, INC.

#### PURPOSE AND POLICY

The primary purpose of the Audit Committee (the “*Committee*”) of Metabasis Therapeutics, Inc. (the “*Company*”) shall be to act on behalf of the Company’s Board of Directors (the “*Board*”) in fulfilling the Board’s oversight responsibilities with respect to the Company’s corporate accounting and financial reporting practices, the Company’s systems of internal accounting and financial controls, audits of the Company’s financial statements, the quality and integrity of the Company’s financial statements and reports, and the qualifications, independence and performance of the certified public accountants engaged as the Company’s independent outside auditors (the “*Auditors*”). The Committee shall also provide oversight assistance in connection with the Company’s legal and ethical compliance programs as established by management and the Board.

The policy of the Committee, in discharging these responsibilities, shall be to maintain and foster an open avenue of communication between the Committee, the Auditors and management.

#### COMPOSITION

The Committee shall consist of at least three members of the Board. All members of the Committee shall satisfy the independence and financial literacy requirements of The Nasdaq National Market (“*Nasdaq*”) applicable to the Committee as in effect from time to time, when and as required by Nasdaq, including any exceptions permitted by these requirements. At least one member shall satisfy the applicable Nasdaq financial experience requirements applicable to the Committee as in effect from time to time, when and as required by Nasdaq, including any exceptions permitted by these requirements. The members of the Committee shall be appointed by and serve at the discretion of the Board. Vacancies occurring on the Committee shall be filled by the Board.

#### ORGANIZATION, MEETINGS AND MINUTES

The Committee’s chairperson shall be designated by the Board or, if it does not do so, the Committee members shall elect a chairperson by vote of a majority of the full Committee. The Chair (or in his or her absence, a member designated by the Chair) shall preside at all meetings of the Committee.

The Committee shall hold such regular or special meetings as its members deem necessary or appropriate. Minutes of each meeting of the Committee shall be prepared and distributed to each director of the Company and the Secretary of the Company promptly after each meeting. The Committee shall report to the Board from time to time and whenever requested to do so by the Board.

#### AUTHORITY

The Committee shall have authority to appoint, determine compensation for and oversee the Auditors as set forth in Section 10A(m)(2) under the Securities Exchange Act of 1934, as amended. The Committee shall have authority to retain and determine compensation for special legal, accounting or other advisors or consultants as it deems necessary or appropriate in the performance of its duties. The Committee shall also have authority to pay ordinary administrative expenses that, as determined by the Committee, are necessary or appropriate in carrying out its duties. The Committee shall have full access to all books, records, facilities and personnel of the Company as deemed necessary or appropriate by the Chair of the Committee to discharge the Committee’s responsibilities hereunder. The Committee shall have authority to require that the Auditors, management and legal counsel, or any other consultant or advisor to the Company attend any meeting of the Committee or meet with any member of the Committee or any of its special legal, accounting or other advisors and consultants.

The operation of the Committee shall be subject to (i) the Bylaws of the Company and (ii) Section 141 of the Delaware General Corporation Law, each as may be in effect from time to time. The approval of this Audit Committee Charter shall be construed as a delegation of authority to the Committee with respect to the responsibilities set forth herein.

## **RESPONSIBILITIES**

The primary responsibility of the Committee shall be to oversee the Company's financial reporting process on behalf of the Board, including the appointment, compensation and oversight of the Auditors, who shall report directly and be accountable to the Committee. The Committee shall report the results of these activities to the Board. The Committee's functions and procedures should remain flexible to address changing circumstances most effectively.

It shall be the responsibility of management to prepare the Company's financial statements and periodic reports and the responsibility of the Auditors to audit those financial statements. These functions shall not be the responsibility of the Committee, nor shall it be the Committee's responsibility to ensure that the financial statements or, if applicable, periodic reports are complete and accurate, conform to generally accepted accounting principles ("*GAAP*") or otherwise comply with applicable laws.

To implement the Committee's purpose and policy, the Committee shall be charged with the following functions and processes, with the understanding, however, that the Committee may supplement or deviate from these activities as appropriate under the circumstances, except as otherwise required by law or the applicable rules of Nasdaq:

1. To evaluate the performance of the Auditors, to assess their qualifications (including their internal quality control procedures and any material issues raised by the Auditors' most recent internal quality control or peer review or any investigations by regulatory authorities) and to determine whether to retain or to terminate the existing Auditors or to appoint and engage new Auditors for the ensuing year.
2. To review, determine and approve the engagement of the Auditors, prior to the commencement of such engagement, to perform all proposed audit, review and attest services, including the scope of and plans for the audit, the adequacy of staffing and the compensation to be paid to the Auditors, which approval may be pursuant to preapproval policies and procedures, including the delegation of preapproval authority to one or more Committee members, provided that all approvals of audit, review and attest services pursuant to such policies and procedures shall be presented to the full Committee at its next meeting.
3. To review, determine and approve the engagement of the Auditors, prior to commencement of such engagement (unless in compliance with exceptions available under applicable laws and rules related to immaterial aggregate amounts of services), to perform any proposed permissible non-audit services, including the scope of the service and the compensation to be paid therefor, which approval may be pursuant to preapproval policies and procedures, including the delegation of preapproval authority to one or more Committee members, provided that all approvals of non-audit services pursuant to such policies and procedures shall be presented to the full Committee at its next meeting.
4. To monitor the rotation of the partners of the Auditors on the Company's audit engagement team as required by law or the applicable rules of Nasdaq.
5. At least annually, to receive and review written statements from the Auditors delineating all relationships between the Auditors and the Company consistent with Independence Standards Board Standard No. 1, to consider and discuss with the Auditors any disclosed relationships and any compensation or services that could affect the Auditors' objectivity and independence, and to assess and otherwise take appropriate action to oversee the independence of the Auditors.

6. To consider and, if deemed appropriate, adopt a policy regarding Committee preapproval of employment by the Company of individuals formerly employed by the Auditors and engaged on the Company's account. Such policy would be restricted to requiring Committee pre-approval only of those individuals who, by their employment, would impact the ability of their former audit firm to continue to provide audit services.
7. To review, upon completion of the annual audit, the financial statements proposed to be included in the Company's Annual Report on Form 10-K to be filed with the Securities and Exchange Commission (the "SEC") and to recommend whether or not such financial statements should be so included.
8. To discuss with the Auditors and management the results of the annual audit, including the Auditors' assessment of the quality (not just acceptability) of accounting principles, the reasonableness of significant judgments and estimates (including material changes in estimates), any audit adjustments noted or proposed by the Auditors (whether "passed" or implemented in the financial statements), the adequacy of the disclosures in the financial statements and any other matters required to be communicated to the Committee by the Auditors under generally accepted auditing standards.
9. To review and discuss with the Auditors and management the results of the Auditors' review of the Company's quarterly financial statements, prior to public disclosure of quarterly financial information, if practicable, or filing with the SEC of the Company's Quarterly Report on Form 10-Q, and any other matters required to be communicated to the Committee by the Auditors under generally accepted auditing standards. The Chair of the Committee may represent the entire Committee for purposes of this discussion.
10. To review and discuss with management and the Auditors, as appropriate, the Company's disclosures contained under the caption "Management's Discussion and Analysis of Financial Condition and Results of Operations" in its periodic reports to be filed with the SEC.
11. To review and discuss with management and the Auditors, as appropriate, earnings press releases as well as the substance of financial information and earnings guidance provided to analysts and ratings agencies, which discussions may be general discussions of the type of information (including the use of pro forma information) to be disclosed or the type of presentation to be made.
12. To review and discuss with management and the Auditors significant issues that arise regarding accounting principles and financial statement presentation, including critical accounting policies and practices or the application of those policies and practices, the potential effect of alternative accounting policies and practices available under GAAP related to material items that have been discussed with management, the potential impact of regulatory and accounting initiatives and any other significant reporting issues and judgments.
13. To review and discuss with management and the Auditors, as appropriate, the Company's guidelines and policies with respect to risk assessment and risk management, including the Company's major financial risk exposures and the steps taken by management to monitor and control these exposures.
14. To evaluate the cooperation received by the Auditors during their audit examination, including any significant difficulties with the audit or any restrictions on the scope of their activities or access to required records, data and information.
15. To review and discuss with the Auditors any management or internal control letter issued or, to the extent practicable, proposed to be issued by the Auditors and management's response, if any, to such letter, as well as any additional material written communications between the Auditors and management.
16. To review and discuss with the Auditors communications between the audit team and the Auditors' national office with respect to accounting or auditing issues presented by the engagement.

17. To review and discuss with the Auditors and management any conflicts or disagreements between management and the Auditors regarding financial reporting, accounting practices or policies and to resolve any conflicts regarding financial reporting.

18. To confer with the Auditors and management regarding the scope, adequacy and effectiveness of financial controls in effect, including any special audit steps taken in the event of material control deficiencies.

19. Periodically, to meet in separate sessions with the Auditors and management to discuss any matters that the Committee, the Auditors or management believe should be discussed privately with the Committee.

20. To consider and review with management, the Auditors and legal counsel, as appropriate, and, in the judgment of the Committee, such special counsel, separate accounting firm and other consultants and advisors as the Committee deems appropriate, any correspondence with regulators or governmental agencies and any published reports, or any other externally distributed documents that incorporate audited or unaudited financial data or that raise material issues regarding the Company's financial statements or accounting policies.

21. To establish procedures for the receipt, retention and treatment of complaints received by the Company regarding financial controls, accounting or auditing matters, including the confidential and anonymous submission by employees of concerns regarding questionable accounting or auditing matters.

22. To review with counsel, the Auditors and management, as appropriate, any significant regulatory or other legal or accounting matters that could have a material impact on the Company's financial statements, compliance programs and policies if, in the judgment of the Committee, such review is necessary or appropriate.

23. To review the results of management's efforts to monitor compliance with the Company's programs and policies designed to ensure adherence to applicable laws and regulations, as well as to its Code of Business Conduct and Ethics, including review and approval of related party transactions to the extent required by Nasdaq rules.

24. To investigate any matter brought to the attention of the Committee within the scope of its duties if, in the judgment of the Committee, such investigation is necessary or appropriate.

25. To prepare the report required by the rules of the SEC to be included in the Company's annual proxy statement.

26. To review and assess the adequacy of this charter annually and recommend any proposed changes to the Board for approval.

27. To report to the Board with respect to material issues that arise regarding the quality or integrity of the Company's financial statements, the Company's compliance with legal or regulatory requirements, the performance or independence of the Auditors or such other matters as the Committee deems appropriate from time to time or whenever it shall be called upon to do so.

28. To review and discuss with management and the Auditors: (i) any material off-balance sheet arrangements or other material financial arrangements of the Company that do not appear on the financial statements of the Company and (ii) any transactions with parties related to or affiliated with the Company which are material in size or involve terms different from those reasonably likely to be negotiated with independent third parties and which transactions are relevant to the understanding of the Company's financial statements.

29. To perform such other functions and to have such powers as may be necessary or appropriate in the efficient and lawful discharge of the foregoing.

## APPENDIX B

### AUDIT AND NON-AUDIT SERVICES PRE-APPROVAL POLICY OF METABASIS THERAPEUTICS, INC.

#### I. STATEMENT OF PRINCIPLES

Under the Sarbanes-Oxley Act of 2002 (the “*Act*”), the Audit Committee (the “*Committee*”) of the Board of Directors of Metabasis Therapeutics, Inc. (the “*Company*”) is responsible for the appointment, compensation and oversight of the work of the Company’s independent outside auditors (the “*Auditors*”). As part of this responsibility, the Committee is required to pre-approve the audit and permissible non-audit services (subject to a *de minimis* exception) performed by the Auditors in order to assure that they do not impair the Auditors’ independence from the Company. To implement these provisions of the Act, the Securities and Exchange Commission (the “*SEC*”) has issued rules specifying the types of services that the Auditors may not provide to their audit clients, as well as the Committee’s administration of the engagement of the Auditors. Accordingly, the Committee has adopted this Audit and Non-Audit Services Pre-Approval Policy (the “*Policy*”), which sets forth the procedures and the conditions pursuant to which services proposed to be performed by the Auditors are, or may be, pre-approved.

Under this Policy, proposed services either may be pre-approved without consideration of specific case-by-case services by the Committee (“*general pre-approval*”), or require the specific pre-approval of the Committee (“*specific pre-approval*”). The Committee believes that the combination of these two approaches in this Policy will result in an effective and efficient procedure to pre-approve services performed by the Auditors. As set forth in this Policy, unless a type of service has received general pre-approval, it will require specific pre-approval by the Committee if it is to be provided by the Auditors. Any proposed services exceeding pre-approved cost levels or budgeted amounts will also require specific pre-approval by the Committee.

For both types of pre-approval, the Committee will consider whether such services are consistent with the SEC’s rules on auditor independence. The Committee will also consider whether the Auditors are best positioned to provide the most effective and efficient service, for reasons such as their familiarity with the Company’s business, people, culture, accounting systems, risk profile and other factors, and whether the service might enhance the Company’s ability to manage or control risk or improve audit quality. All such factors will be considered as a whole, and no one factor should necessarily be determinative.

The Committee is also mindful of the relationship between fees for audit and non-audit services in deciding whether to pre-approve any such services and may determine, for each fiscal year, the appropriate ratio between the total amount of fees for Audit, Audit-related and Tax services and the total amount of fees for certain permissible non-audit services classified as All Other services.

The appendices to this Policy describe the Audit, Audit-related, Tax and All Other services that have the general pre-approval of the Committee. The term of any general pre-approval is 12 months from the date of pre-approval, unless the Committee considers a different period and states otherwise. The Committee will annually review and pre-approve the services that may be provided by the Auditors without obtaining specific pre-approval from the Committee. The Committee will add or subtract to the list of general pre-approved services from time to time, based on subsequent determinations.

The purpose of this Policy is to set forth the procedures by which the Committee intends to fulfill its responsibilities. It does not delegate the Committee’s responsibilities to pre-approve services performed by the Auditors to management.

The Auditors have reviewed this Policy and believe that implementation of the policy will not adversely affect their independence.

## II. DELEGATION

As provided in the Act and the SEC's rules, the Committee may delegate either type of pre-approval authority to one or more of its members. The member to whom such authority is delegated must report, for informational purposes only, any pre-approval decisions to the Committee at its next scheduled meeting.

## III. AUDIT SERVICES

The annual Audit services engagement terms and fees will be subject to the specific pre-approval of the Committee. Audit services include the annual financial statement audit (including required quarterly reviews) and other procedures required to be performed by the Auditors to be able to form an opinion on the Company's financial statements. These other procedures include information systems and procedural reviews and testing performed in order to understand and place reliance on the systems of internal control, and consultations relating to the audit or quarterly review. Audit services also include the attestation engagement for the Auditors' report on management's report on internal controls for financial reporting, once required. The Committee will monitor the Audit services engagement as necessary, but no less than on a quarterly basis, and will also specifically pre-approve, if necessary, any changes in terms, conditions and fees resulting from changes in audit scope, Company structure or other items.

In addition to the annual Audit services engagement specifically pre-approved by the Committee, the Committee may grant general pre-approval to other Audit services, which are those services that only the Auditors reasonably can provide. Other Audit services may include statutory audits and services associated with SEC registration statements, periodic reports and other documents filed with the SEC or other documents issued in connection with securities offerings.

The Committee has generally pre-approved the Audit services listed in **Appendix A**. All other Audit services not listed in **Appendix A** must be specifically pre-approved by the Committee.

## IV. AUDIT-RELATED SERVICES

Audit-related services are assurance and related services that are reasonably related to the performance of the audit or review of the Company's financial statements or that are traditionally performed by the Auditors. Because the Committee believes that the provision of Audit-related services does not impair the independence of the auditor and is consistent with the SEC's rules on auditor independence, the Committee may grant general pre-approval to Audit-related services. Audit-related services include, among others, due diligence services pertaining to potential business acquisitions/dispositions; accounting consultations related to accounting, financial reporting or disclosure matters not classified as "Audit services"; assistance with understanding and implementing new accounting and financial reporting guidance from rulemaking authorities; financial audits of employee benefit plans; agreed-upon or expanded audit procedures related to accounting and/or billing records required to respond to or comply with financial, accounting or regulatory reporting matters; and assistance with internal control reporting requirements.

The Committee has generally pre-approved the Audit-related services listed in **Appendix A**. All other Audit-related services not listed in **Appendix A** must be specifically pre-approved by the Committee.

## V. TAX SERVICES

The Committee believes that the Auditors can provide Tax services to the Company such as tax compliance, tax planning and tax advice without impairing the auditor's independence, and the SEC has stated that the Auditors may provide such services. Hence, the Committee believes it may grant general pre-approval to those Tax services that have historically been provided by the auditor, that the Committee has reviewed and believes would not impair the independence of the auditor, and that are consistent with

the SEC's rules on auditor independence. The Committee will not permit the retention of the Auditors in connection with a transaction initially recommended by the Auditors, the sole business purpose of which may be tax avoidance and the tax treatment of which may not be supported in the Internal Revenue Code and related regulations. The Committee will consult with the Company's Chief Financial Officer or outside counsel to determine that the tax planning and reporting positions are consistent with this policy.

Pursuant to the preceding paragraph, the Committee has generally pre-approved the Tax services listed in **Appendix A**. All Tax services not listed in **Appendix A** must be specifically pre-approved by the Committee, including tax services proposed to be provided by the Auditors to any executive officer or director of the Company, in his or her individual capacity, where such services are paid for by the Company.

#### **VI. ALL OTHER SERVICES**

The Committee believes, based on the SEC's rules prohibiting the Auditors from providing specific non-audit services, that other types of non-audit services are permitted. Accordingly, the Committee believes it may grant general pre-approval to those permissible non-audit services classified as All Other services that it believes are routine and recurring services, would not impair the independence of the auditor and are consistent with the SEC's rules on auditor independence.

The Committee has generally pre-approved the All Other services listed in **Appendix A**. Permissible All Other services not listed in **Appendix A** must be specifically pre-approved by the Committee.

A list of the SEC's prohibited non-audit services is attached to this policy as **Exhibit 1**. The SEC's rules and relevant guidance should be consulted to determine the precise definitions of these services and the applicability of exceptions to certain of the prohibitions.

#### **VII. PRE-APPROVAL FEE LEVELS OR BUDGETED AMOUNTS**

Pre-approval fee levels or budgeted amounts for all services to be provided by the Auditors will be established annually by the Committee. Any proposed services exceeding these levels or amounts will require specific pre-approval by the Committee. The Committee is mindful of the overall relationship of fees for audit and non-audit services in determining whether to pre-approve any such services. For each fiscal year, the Committee may determine the appropriate ratio between the total amount of fees for Audit, Audit-related and Tax services, and the total amount of fees for services classified as All Other services.

#### **VIII. PROCEDURES**

With respect to any services to be provided by the Auditors for which pre-approval by the Committee is proposed, the Auditors must provide to the Committee a detailed description of the services to be rendered. The Committee will be informed on a timely basis of any services rendered by the Auditors pursuant to this Policy.

Requests or applications to provide services that require specific pre-approval by the Committee will be submitted to the Committee by both the Auditors and the Chief Financial Officer, and must include a joint statement as to whether, in their view, the request or application is consistent with the SEC's rules on auditor independence.

The Committee has designated the Chief Financial Officer to monitor the performance of all services provided by the Auditors and to determine whether this Policy is being appropriately implemented. The Chief Financial Officer will report to the Committee on a periodic basis on the results of such monitoring. Both the Chief Financial Officer and management will immediately report to the Chair of the Committee any breach of this policy that comes to the attention of the Chief Financial Officer or any member of management.

**APPENDIX A**

**GENERALLY PRE-APPROVED SERVICES FOR FISCAL YEAR 2005**

<u>Pre-Approved Service</u>	<u>Pre-Approved Fees</u>
<b>Audit Services</b>	
Audit of financial statements, fourth quarter review, and procedures related to filing of related 10-K	\$89,000
Timely required quarterly reviews in accordance with SAS 100	\$12,750 per quarter
Services associated with SEC registration statements (S-8, S-3, etc.), periodic reports and other documents filed with the SEC or other documents issued in connection with securities offerings (e.g., comfort letters, consents), and assistance in responding to SEC comment letters	Up to \$25,000
<b>Audit-related Services</b>	
Consultations by the Company's management as to the accounting or disclosure treatment of transactions or events and/or the actual or potential impact of final or proposed rules, standards or interpretations by the SEC, FASB, or other regulatory standard setting bodies (Note: Under SEC rules, some consultations may be "Audit services" rather than "Audit-related" services)	Up to \$25,000
General assistance with implementation of the requirements of SEC rules or listing standards promulgated pursuant to the Sarbanes-Oxley Act, including consultations on the Company's implementation of and compliance with Section 404 of the Sarbanes-Oxley Act	Up to \$20,000
<b>Tax Services</b>	
Preparation of U.S. federal income tax return on Form 1120, state and local income and franchise tax returns for California for the year ended December 31, 2004	TBD
General tax consultation regarding federal and state income tax matters, employment tax matters and sales and use tax matters	TBD
<b>All Other Services</b>	
Subscription to Ernst & Young Online, a proprietary knowledge management and research system	Up to \$3,500

Note: Out-of-pocket expenses will be billed in addition to fees.

**EXHIBIT 1**

**PROHIBITED NON-AUDIT SERVICES**

Bookkeeping or other services related to the accounting records or financial statements of the audit client  
Financial information systems design and implementation  
Appraisal or valuation services, fairness opinions or contribution-in-kind reports  
Actuarial services  
Internal audit outsourcing services  
Management functions  
Human resources  
Broker-dealer, investment adviser or investment banking services  
Legal services  
Expert services unrelated to the audit

**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)

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

For the fiscal year ended December 31, 2004

**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  
(State or other jurisdiction  
of incorporation or organization)

33-0753322  
(I.R.S. Employer Identification No.)

9390 Towne Centre Drive, Building 300, San Diego, CA  
(Address of principal executive offices)

92121  
(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: (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  No

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.

Indicate by check mark whether the registrant is an accelerated filer (as defined in Rule 12b-2 of the Exchange Act).  
Yes  No

As of June 30, 2004, 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 \$56.9 million, based on the closing price of the registrant's common stock on the Nasdaq National Market on June 30, 2004 of \$6.95 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, 2005 was 18,180,482.

**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, 2004 are incorporated by reference into Part III of this report.

**METABASIS THERAPEUTICS, INC.**  
**FORM 10-K—ANNUAL REPORT**  
**FOR THE YEAR ENDED DECEMBER 31, 2004**

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## 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," "should," "will," "would" or similar expressions.

Forward-looking statements involve known and unknown risks, uncertainties and other factors which may cause our actual results, performance or achievements to be materially different from any future results, performances or achievements expressed or implied by the forward-looking statements. We discuss these risks in greater detail in 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 small molecule drugs principally to treat metabolic diseases, cancer and certain other diseases linked to pathways in the liver. Examples of common metabolic diseases include diabetes, hyperlipidemia, a disease involving elevated levels of lipids such as cholesterol, and obesity. 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 three product candidates in clinical development, CS-917, pradefovir and MB07133, indicated for the treatment of type 2 diabetes, hepatitis B and primary liver cancer, respectively. Recently, three clinical trials of CS-917 were halted due to two serious adverse events described below that occurred in a clinical trial combining CS-917 with the marketed diabetes treatment metformin. CS-917 is being developed in collaboration with Sankyo Co., Ltd. Sankyo is responsible for clinical development of the drug. Sankyo has informed us that one Phase I clinical trial of CS-917 is continuing and that one or more additional Phase I clinical trials may be initiated soon to further evaluate the product candidate. The continuing Phase I clinical trial does not combine CS-917 with metformin. In parallel with this activity, we and Sankyo, together and separately, are evaluating the next steps, if any, to be taken in this program.

Our three product candidates currently in clinical development are:

- *CS-917, a product candidate for the treatment of type 2 diabetes.* CS-917 is being developed in collaboration with Sankyo Co., Ltd. In addition to having responsibility for clinical development of the drug, 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 diabetics, this pathway produces excessive amounts of glucose, contributing to high blood glucose levels which in turn may lead to morbidity and death. Results

from a 14-day Phase II clinical trial and a 28-day Phase II clinical trial, both in type 2 diabetics, 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 Sankyo Company, Ltd., our collaborator with respect to the development of CS-917.

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. A third clinical trial was initiated in February 2005 to evaluate the interaction of CS-917 with the marketed diabetes drug metformin. In March 2005, we were notified by Sankyo that two serious adverse events involving lactic acidosis, a serious and potentially fatal condition, had occurred in the clinical trial evaluating the interaction of CS-917 with the marketed diabetes drug metformin. The serious adverse events were resolved after medical intervention. The two patients were administered CS-917 in combination with metformin. These three clinical trials have been stopped. Sankyo has informed us that one Phase I clinical trial of CS-917 is continuing and that one or more additional Phase I clinical trials may be initiated soon to further evaluate the product candidate. The continuing Phase I clinical trial does not combine CS-917 with metformin. In parallel with this activity, we and Sankyo, together and separately, are evaluating the next steps, if any, to be taken in this program.

These findings could have significant adverse implications for our business. For a discussion of these implications, see the section in "Risk Factors" entitled "*Recent serious adverse events observed during a clinical trial of CS-917 may have a significant adverse impact on our business.*"

- *Pradefovir mesylate, a product candidate for the treatment of hepatitis B that is currently in Phase II clinical trials.* Pradefovir uses our HepDirect technology to target the active form of Hepsera, a marketed anti-viral drug indicated for the treatment of hepatitis B, specifically to the liver. The active form of Hepsera is known as adefovir. Hepsera also delivers adefovir but throughout the body, rather than specifically to the liver. We believe that Hepsera, while effective against 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 active drug may be achieved without causing kidney toxicity, thereby providing greater efficacy. Pradefovir has completed two Phase I clinical trials in healthy volunteers in which it was well tolerated and exhibited favorable pharmacokinetics and two Phase I clinical trials designed to evaluate safety and preliminary efficacy in a limited number of patients, one in the U.S. and one in Taiwan. Pradefovir was well tolerated in these clinical trials and it significantly lowered the level of hepatitis B virus in patients in each of the dose groups evaluated, compared to patients treated with a placebo. Based on these initial results, 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 12-month dose-ranging Phase II clinical trial of pradefovir. This Phase II clinical trial will include an interim analysis after six months of dosing, the purpose of which will be to select appropriate doses for potential Phase III clinical trials. The dose-ranging Phase II clinical trial will then continue until all patients are dosed for 12 months in order to collect additional information on safety and efficacy. Based on the decision to initiate this Phase II clinical trial, we earned a \$1 million milestone payment from Valeant. This dose-ranging Phase II clinical trial was fully enrolled as of November 2004. Pradefovir was formerly called remofovir and before that, Hepavir B.
- *MB07133, a product candidate for the treatment of primary liver cancer that is currently in a Phase I 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, a marketed

anti-cancer drug, to the liver while decreasing levels of the active form of the drug in tissues outside of the liver. We believe this unique liver-targeting property will enhance efficacy 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 exclusive worldwide commercialization rights to MB07133.

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, processes referred to as drug uptake, metabolism and excretion, respectively. With this knowledge, we developed proprietary technologies, including two named 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 we are also using it in certain of our advanced research programs.

We use our HepDirect technology to target drugs 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 may significantly improve drug efficacy and safety over other 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, we have a collaboration with Merck & Co., Inc. 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, which are research programs in which we have identified lead drug compounds and shown them to have efficacy in animal models, have the potential to yield additional clinical development candidates within the next two years. Once recommended, a clinical development candidate undergoes pre-clinical development including scale up, toxicology and formulations development. Successful compounds would then enter human clinical testing.

One of these advanced research programs yielded a compound, MB07803, that we recommended for clinical development in the first quarter of 2004. MB07803 is a clinical development candidate for the treatment of type 2 diabetes that works by the same mechanism as CS-917. We had planned to begin clinical development of MB07803 in the first half of 2005. However, we have placed further development of MB07803 on hold pending the outcome of our evaluation of the recently reported serious adverse events related to CS-917. Metabasis retains all rights to MB07803.

We have several advanced research programs that we believe have the potential to yield additional clinical development candidates within the next two years. These advanced research programs include:

- a program targeting hyperlipidemia and possibly obesity 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,
- programs using our HepDirect and other liver-targeting technology to identify drugs to treat hepatitis C infection, including a collaboration with Merck to apply our technology to certain compounds Merck has studied for the treatment of hepatitis C infection,
- a program using our NuMimetic technology 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 HepDirect partnerships, 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 the majority of patients. Some existing anti-viral and anti-cancer drugs, while effective outside of the liver, 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. 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.

### Our Pipeline

The following table summarizes our product candidates currently in clinical development and advanced research programs:

#### Pipeline 2004

PROGRAMS/PRODUCTS <sup>(1)</sup>	DISCOVERY	LEAD COMPOUND OPTIMIZATION	PRE-CLINICAL	PHASE I	PHASE II	PHASE III	MARKET	OUR COMMERCIAL RIGHTS
Diabetes CS-917	DEVELOPMENT UNDER REVIEW <sup>(4)</sup>							North America Co-promotion, Rest of World Royalties
Hepatitis B Pradefovir mesylate	[Progress bars]							Royalties
Primary Liver Cancer MB07133	[Progress bars]							Worldwide
Diabetes MB07803	DEVELOPMENT ON HOLD <sup>(4)</sup>							Worldwide
Hyperlipidemia MB07811 <sup>(2)</sup>	[Progress bars]							Worldwide
Diabetes/Hyperlipidemia Unnamed	[Progress bars]							Worldwide
Hepatitis C Unnamed <sup>(3)</sup>	[Progress bars]							Royalties
Liver Fibrosis MB07100 <sup>(2)</sup>	[Progress bars]							Worldwide

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

(2) This is the lead compound we are currently studying in our advanced research program for the treatment of the disease listed.

(3) We are collaborating with Merck to apply our HepDirect technology to certain compounds Merck has studied for the treatment of hepatitis C infection.

(4) CS-917 and MB07803 Diabetes programs are currently under review due to certain safety issues. These findings could have significant adverse implications for our business. For a discussion of these implications, see the section in "Risk Factors" entitled "Recent serious adverse events observed during a clinical trial of CS-917 may have a significant adverse impact on our business."

### 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. Recently, three studies on CS-917 were halted due to two serious adverse events described below that occurred in a clinical trial combining CS-917 with the marketed diabetes treatment metformin. Sankyo has informed us that one Phase I clinical trial with CS-917 is continuing and that one or more additional Phase I clinical trials may be initiated soon to further evaluate the product candidate. The continuing Phase I clinical trial does not combine CS-917 with metformin. In parallel with this activity, we and Sankyo, together and separately, are evaluating the next steps, if any, to be taken in this program. CS-917 was in Phase II clinical development at the time the serious adverse events occurred.

We believe 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 significantly reduced the elevated blood glucose levels that characterize type 2 diabetes. CS-917 is being developed in partnership with Sankyo, and we retain co-promotion rights in North America.

### *Diabetes*

There are two forms of diabetes: type 1 or insulin dependent, juvenile onset diabetes, and type 2 or adult onset diabetes. Approximately 90% of diabetes patients have type 2 diabetes. Elevated blood glucose levels in type 2 diabetics 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. In addition, diabetes is a leading cause of death in the U.S.

Type 2 diabetes afflicts over 160 million people worldwide, with over 18 million afflicted in the U.S. Global sales of oral diabetes drugs currently exceed \$9 billion annually, with the U.S. accounting for over 70% 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, a standard measure of glucose control, be maintained under 7% in type 2 diabetics. 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 is associated with a significant risk of hypoglycemia.
- insulin sensitizers, which lower glucose levels by enhancing insulin sensitivity. This drug class is associated with fluid retention and anemia. In addition, the U.S. Food and Drug Administration, or FDA, requires liver function monitoring for patients using insulin sensitizers to protect against liver toxicity.
- 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 24%, 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 is associated with an increased risk of lactic acidosis in certain patient populations, especially patients with kidney dysfunction. In addition, metformin therapy commonly leads to transient gastrointestinal disturbances such as nausea, diarrhea and vomiting, which can compromise patient compliance.

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

diabetics. 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 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 diabetics will require multiple oral drug therapies to attain adequate glucose control and just over 30% of type 2 diabetics will ultimately advance to a stage that requires daily insulin injections. Because the disease is so poorly treated with currently marketed drugs, the diabetes market is receptive to new drugs and new approaches have experienced rapid uptake.

### *CS-917*

Studies show that the elevated blood glucose levels that characterize type 2 diabetics 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 diabetics. Pharmaceutical companies have tried to find inhibitors of FBPase, but 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.

We believe that if CS-917 can be safely administered, it 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 insulin secretion enhancers, CS-917 does not cause weight gain in animals and is therefore expected to be effective in obese diabetics. Studies also show that CS-917 is effective in animal models of lean diabetes. In addition, glucose lowering occurs independent of insulin levels, suggesting that CS-917 may exhibit glucose lowering activity in advanced diabetics, a patient population commonly resistant to therapies dependent on insulin production such as insulin sensitizers and insulin secretion enhancers.

### *Clinical Trials*

To date, our partner Sankyo has completed a number of Phase I clinical trials in healthy volunteers as well as Phase I and Phase II clinical trials in type 2 diabetics.

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 diabetics with CS-917 or a placebo once daily for 14 days using a randomized, placebo-controlled, double-blind study 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 study 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 study initiation) in patients treated with CS-917, as compared to the change from baseline levels in patients treated with a placebo. The primary efficacy endpoint of the study, which was achieved, was 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. 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 diabetics 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 study design. The primary efficacy endpoint of the study 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 that 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 proven.

The inhibition of gluconeogenesis can cause elevated levels of lactic acid, or lactate, which, if high and sustained, under certain conditions can lead to lactic acidosis, a serious and potentially fatal condition. Certain pre-clinical trials have shown that CS-917 raises lactate levels two- to three-fold in some but not all animal models at glucose lowering doses. 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. The other six patients in this dose group as well as patients administered lower doses of CS-917 showed lactate levels within the normal range. 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 study. However, one patient who received 200 milligrams of CS-917 twice a day was withdrawn from the study by the investigator on day 15 due to concerns over consistently elevated lactate levels measured the previous day.

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. A third clinical trial was initiated in February 2005 to evaluate the interaction of CS-917 with the marketed diabetes drug metformin. In March 2005, we were notified by Sankyo that two serious adverse events involving lactic acidosis, a serious and potentially fatal condition, had occurred in the clinical trial evaluating the interaction of CS-917 with the marketed diabetes drug metformin. The serious adverse events were resolved after medical intervention. The two patients were administered CS-917 in combination with metformin. These three clinical trials have been stopped. Sankyo has informed us that one Phase I clinical trial of CS-917 is continuing and that one or more additional Phase I clinical trials may be initiated soon to further evaluate the product candidate. The continuing Phase I clinical trial does not combine CS-917 with metformin. In parallel with this activity, we and Sankyo, together and separately, are evaluating the next steps, if any, to be taken in this program. In addition, we are evaluating the impact on our second generation treatment for diabetes, MB07803, which is believed to have the same therapeutic mechanism as CS-917.

It is also possible that CS-917 may cause other side effects. In certain pre-clinical studies, as expected based on the mechanism of the compound, 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 and/or decreasing other glucose-producing mechanisms in the body, especially in elderly patients who are

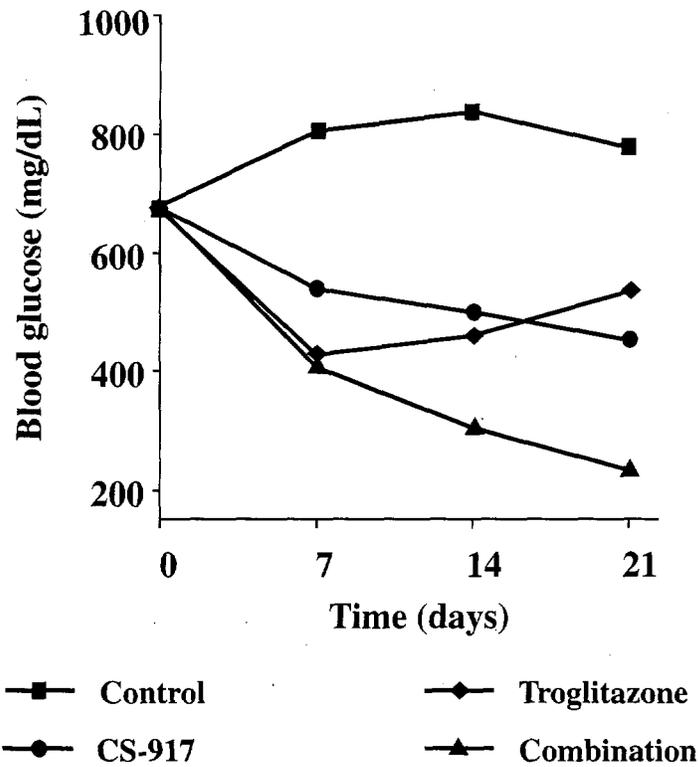
already prone to develop this condition. Some rodent models of diabetes studied in pre-clinical trials of CS-917 demonstrated, at glucose lowering doses, increased levels of fat molecules known as triglycerides, which are associated with an increased risk of cardiovascular disease. Elevated triglyceride levels have not been observed in either the 14-day or 28-day clinical trials described above. Other side effects observed during early clinical trials of CS-917 included nausea and vomiting.

These findings could have significant adverse implications for our business. For a discussion of these implications, see the section in "Risk Factors" entitled "*Recent serious adverse events observed during a clinical trial of CS-917 may have a significant adverse impact on our business.*"

#### *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 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 insulin secretion enhancers, CS-917 induced no weight gain in treated animals relative to untreated animals.

Pre-clinical studies demonstrated that the combination of maximally effective doses of an insulin sensitizer with an FBPase inhibitor results in even greater efficacy than either dose 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 of glucose 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 combined FB Pase inhibitors with other marketed insulin sensitizers with similar results.

Pre-clinical studies in diabetes animal models support the use of CS-917 in advanced diabetics. 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, which shows glucose lowering effects in both advanced stage and early stage animal models of the disease.

In addition, 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, Sankyo moved CS-917 into clinical trials in July 2001.

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

Pradefovir mesylate is an oral product candidate that is in Phase II clinical trials for hepatitis B, a serious liver infection. Pradefovir has been studied in two Phase I clinical trials designed to evaluate safety and preliminary efficacy in a limited number of patients. Although several marketed drugs target hepatitis B, the disease remains poorly treated. A recently approved hepatitis B drug is Hepsera. Hepsera is 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, uses 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 significantly reducing dose-related toxicities. In pre-clinical and clinical studies, pradefovir has been shown to be well-tolerated and to result in elevated levels of the active form of adefovir in the liver without significantly increased levels in other tissues. We are developing pradefovir in partnership with Valeant, to whom we have 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 350 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 comprise 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 90% 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 distinct shortcomings. 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. To our knowledge, all hepatitis B drugs that are currently in late stage clinical development have also been shown to induce viral resistance. 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.

Hepsera and lamivudine both decrease virus levels, as measured by hepatitis B DNA in the blood serum. Nevertheless, further decreases are desirable since these reductions are not 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 of Hepsera led to a more than ten-fold greater reduction in hepatitis B DNA in the blood serum 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 Hepsera is only prescribed in suboptimal dosages for the reduction of virus levels.

### *Pradefovir*

Pradefovir and Hepsera are both prodrugs of adefovir. A prodrug is a drug to which a chemical modification has been made that renders the target drug inactive until enzymes in the body convert it to its active form. When produced in patients with hepatitis B, adefovir acts in the liver and leads to decreased virus levels. Pradefovir is a HepDirect prodrug that produces adefovir predominantly in the liver, where the virus resides, while Hepsera produces adefovir throughout the body. We expect that, as a result of this difference in distribution, pradefovir will improve efficacy in the treatment of hepatitis B relative to Hepsera.

### *Clinical Trials*

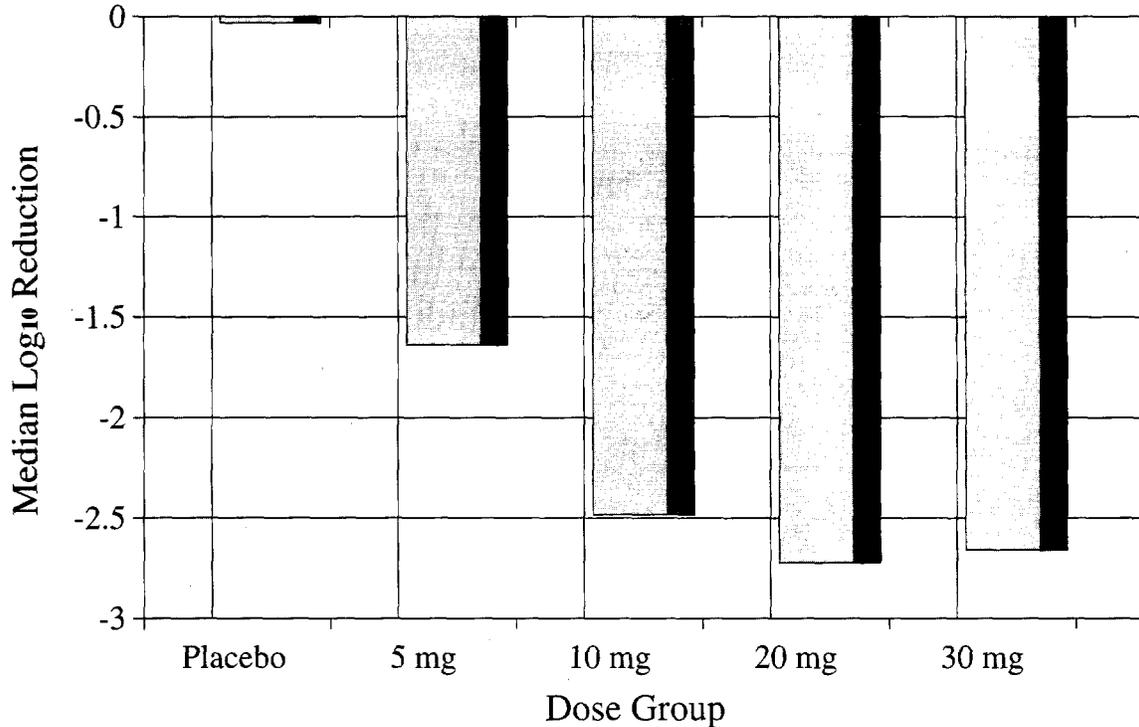
Valeant has completed two single-dose Phase I clinical trials of pradefovir in 47 healthy volunteers. Pradefovir was well tolerated at all dose levels and demonstrated a good pharmacokinetic profile in these clinical trials. These clinical trials also confirmed that pradefovir appeared to be converted 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 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. The following chart shows the efficacy achieved in the 28-day Taiwanese clinical trial described above, as

demonstrated by a log reduction of serum hepatitis B virus DNA levels from baseline levels at clinical trial initiation in the four dose groups tested versus placebo:

### Effect of Pradefovir on Viral DNA Levels

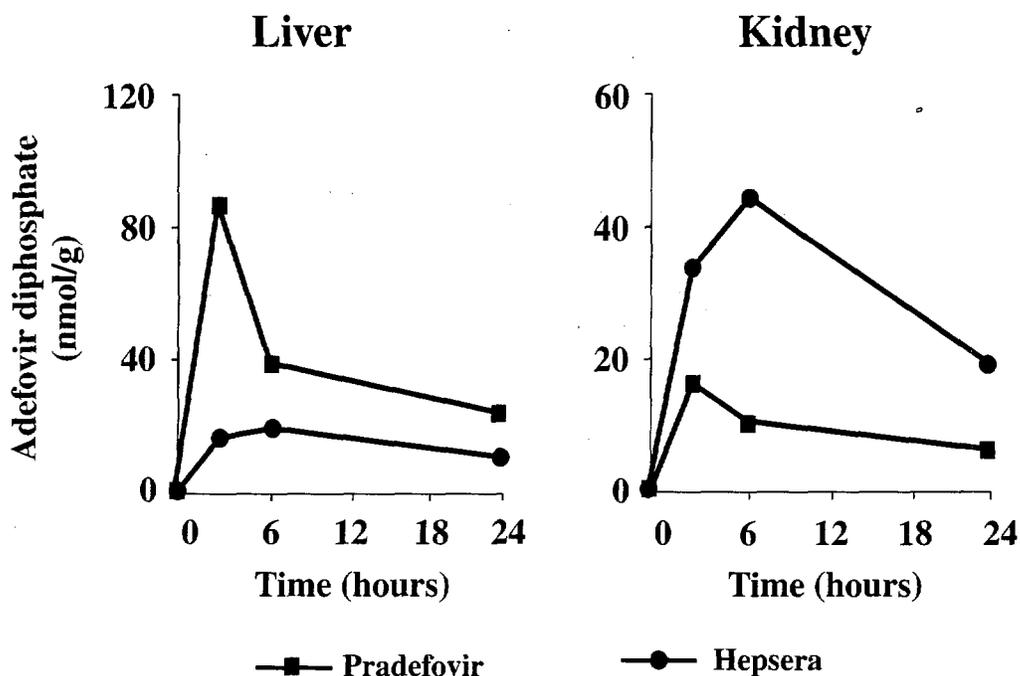
28-Day Taiwanese Clinical Trial



Based on these initial results, in July 2004 Valeant commenced a 12-month dose-ranging Phase II clinical trial of pradefovir which will include an interim analysis after six months of dosing, the purpose of which will be to select appropriate doses for potential Phase III clinical trials and to allow for the possible commencement of these Phase III clinical trials before completion of the Phase II clinical trial. This Phase II clinical trial was fully enrolled as of November 2004.

#### *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.



The improvement in liver to kidney distribution resulting from treatment with pradefovir in comparison to Hepsera was also demonstrated in a study in rats using whole body autoradiography, a process in which a radioactive marker was included with the drugs when administered and the radioactivity of the rats was later analyzed to determine the distribution of adefovir and related metabolites in their bodies. At various times after dosing, rats treated with pradefovir exhibited high levels of adefovir and related metabolites in the liver relative to the kidney, whereas rats dosed with a similar amount of Hepsera showed high levels of adefovir and related metabolites in the kidney relative to the liver.

We believe that pradefovir achieves higher liver levels of adefovir and related metabolites relative to Hepsera because pradefovir more readily distributes into the liver where it is specifically converted to adefovir which is then converted to adefovir diphosphate. Moreover, unlike Hepsera, pradefovir is not readily converted to adefovir in the blood, intestine and kidney. Since kidney exposure to adefovir is implicated in kidney toxicity, decreased kidney exposure may result in a safer drug. This expectation was supported by 28-day toxicology studies in rats and monkeys, which showed pradefovir to have a significantly better safety profile than Hepsera, based on findings showing that pradefovir's highest non-toxic dose was approximately 7.5-fold higher than the non-toxic dose for Hepsera in each species.

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

MB07133 is an intravenously administered product candidate in a Phase I 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 is a HepDirect prodrug of araC, an anti-cancer drug that is used to treat leukemia but is ineffective against primary liver cancer. AraC's anti-cancer activity is associated with its ability to be converted to its biologically active form, araCTP. In contrast to araC, MB07133 uses our HepDirect technology to target an activated form of araC to the liver, where it is rapidly converted to araCTP, thereby providing a means to treat primary liver cancer. We have retained full worldwide commercialization 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 thirteenth leading cause of cancer mortality in women. In 2003 the American Cancer Society estimated that approximately 15,000 new cases of primary liver cancer were diagnosed per year in the U.S. Primary liver cancer is responsible for over 500,000 deaths 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 is a HepDirect prodrug of araC, a well known off-patent oncolytic drug used for the treatment of 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 drug compound that results in 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

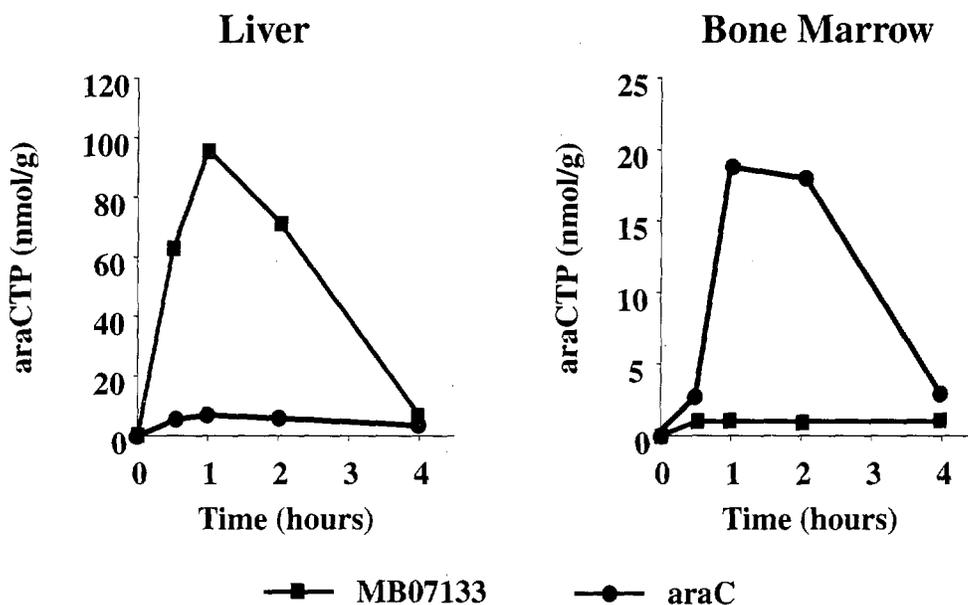
change in distribution of araCTP will maximize MB07133's potential therapeutic effect on liver tumors while minimizing its toxicity.

### Clinical Trials

In September 2003 we initiated a Phase I 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. and Hong Kong. The study is an open label, dose escalation Phase I 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 up to a total of six infusions of MB07133. The goal of the Phase I 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. We believe we have made good progress toward establishing the maximum tolerated dose in this trial. 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 show that relative to araC, MB07133 will deliver therapeutically active levels of araCTP to human primary liver cancer tumors with less toxicity.

### **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.

In addition to our advanced research programs, we have a program focused on the discovery of liver-targeted antivirals for the treatment of hepatitis C. In 2003 we received a Small Business Innovation Research grant for this program providing funding of up to \$2.4 million over a two-year period. We granted Merck a time-limited, exclusive option to obtain a license to develop and commercialize certain compounds we discover through this program. Other than these license rights and Merck's rights to commercialize product candidates developed in our collaboration with Merck for the treatment of hepatitis C, we retain worldwide commercialization rights for all product candidates developed in our current research programs.

We believe our advanced research programs have the potential to yield additional clinical development candidates within the next two years. One of these advanced research programs yielded a compound, MB07803, that we recommended for clinical development in the first quarter of 2004. MB07803 is a clinical development candidate for the treatment of type 2 diabetes that works by the same mechanism as CS-917. We have placed further development of MB07803 on hold pending the outcome of our evaluation of the recently reported serious adverse events related to CS-917.

Our advanced research programs include:

#### *A compound for the treatment of hyperlipidemia and the possible treatment of obesity*

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 are developing compounds that are designed to control the expression of genes in the liver that are important for making or using cholesterol as well as genes involved in the control of energy expenditure. We have discovered a series of compounds that exhibit high liver specificity in animals and demonstrated the

ability of these compounds to lower cholesterol in animals without causing toxicities associated with previously discovered compounds in the same class. We intend to use these compounds to treat patients with hyperlipidemia and are also testing the potential of these compounds to treat obesity. Our lead compound from this research program is MB07811.

*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 which 2.7 million are chronically infected.

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 will make and conduct initial testing of resulting antiviral compounds. All of our activities under the collaboration are being funded by Merck. In addition, 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 in the liver known to regulate cholesterol and fat levels. We have shown in animal models that our lead compound from this research program inhibits cholesterol and fat synthesis. We believe that this compound or a related compound will be useful for the treatment of patients with type 2 diabetes, hyperlipidemia or non-alcoholic steatohepatitis. This nucleotide mimetic is designed to target type 2 diabetes by a different mechanism than CS-917 and MB07803.

*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 were 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 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. Our lead compound from this research program is MB07100.

**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*

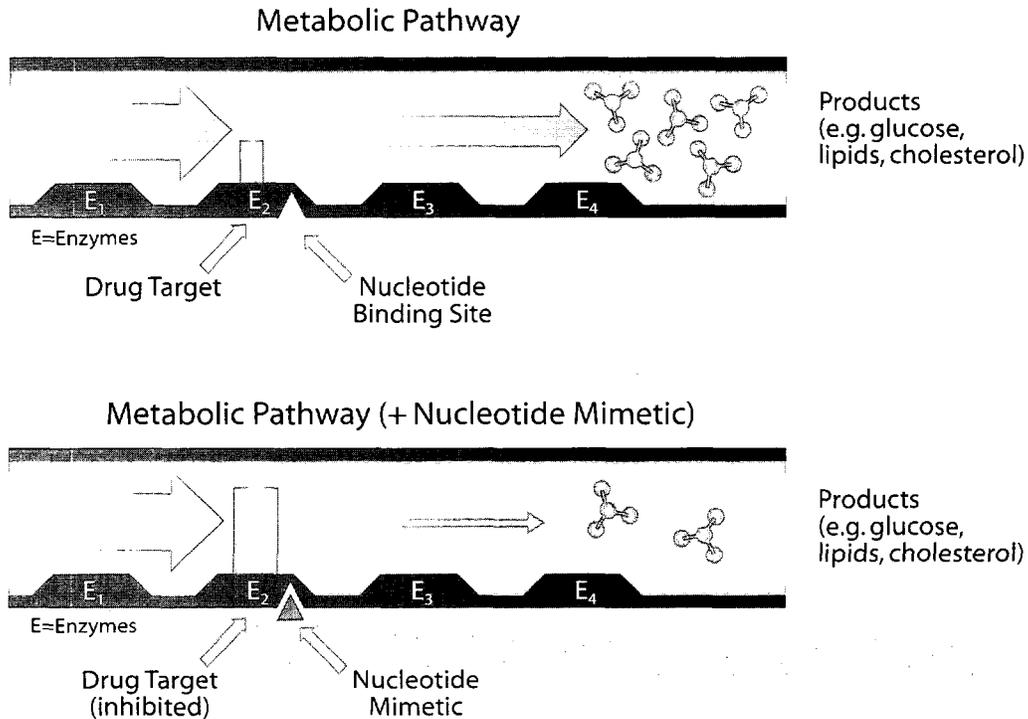
The liver plays a central role in many metabolic diseases. Metabolic pathways that reside in the liver are responsible for much of the body's generation of products such as cholesterol, glucose and lipids. This production is normally dependent on an individual's nutritional and hormonal status. However, 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 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 now becoming 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 enzyme activity and therefore the rate of flow 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 effectiveness 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 shows how our NuMimetic technology works:

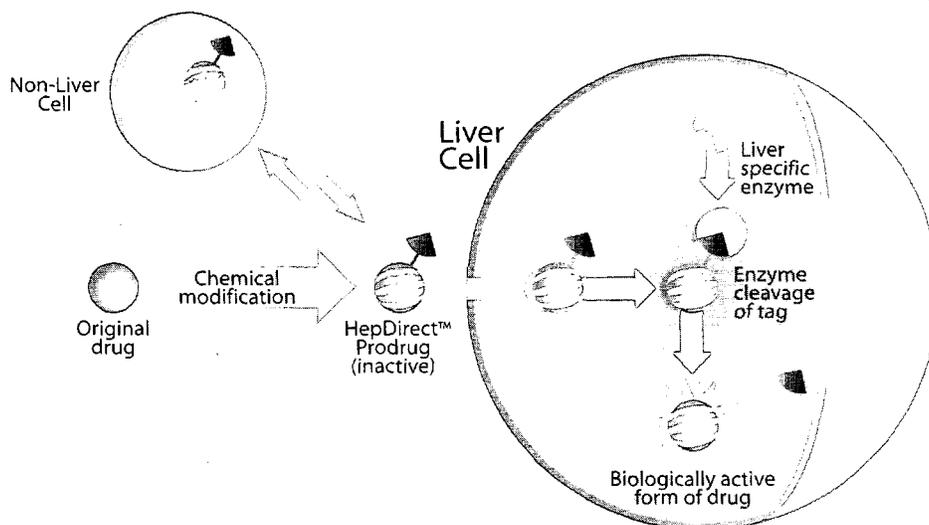


*HepDirect Technology*

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 by making a simple chemical modification that renders the target

drug biologically inactive. We refer to the modified drug as a HepDirect prodrug. The following diagram shows 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 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 will 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. We are using this technology and other liver-targeting technologies in a collaboration with Merck in which we are creating prodrugs of certain compounds that Merck is supplying to us. These compounds target the hepatitis C virus residing in the liver.

#### *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 three product candidates in clinical development, CS-917, pradefovir and MB07133, indicated for the treatment of type 2 diabetes, hepatitis B and primary liver cancer, respectively. Recently, three studies on CS-917 were halted due to two serious adverse events described below that occurred in a clinical trial combining CS-917 with the marketed diabetes treatment metformin. We and Sankyo, together and separately, are evaluating the next steps, if any, to be taken in this program. CS-917 was in Phase II clinical development at the time the serious adverse events occurred. We were responsible for the discovery and initial development of each of these products. Sankyo and Valeant are primarily responsible for further clinical development of CS-917 and pradefovir, respectively. We participate on joint development teams, and we retain significant commercial interest in both products, including North American co-promotion rights for CS-917. We are solely responsible for the development of 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 2004, we recommended the clinical development of MB07803, a product candidate for the treatment of type 2 diabetes that, like CS-917, is designed to block the metabolic pathway in the liver that is responsible for producing glucose. We have placed further development of MB07803 on hold pending the outcome of our evaluation of the recently reported serious adverse events related to CS-917. We also have an advanced research program for the treatment of type 2 diabetes by a different mechanism than CS-917 and MB07803, as well as an advanced research program for the treatment of hyperlipidemia that may yield additional new drug compounds for clinical development. We retain worldwide commercialization rights for all product candidates developed in our current research and advanced research programs, with the exception of products resulting from our collaboration with Merck, and an exclusive option we granted to Merck to obtain a license to develop and commercialize certain compounds we discover through our internal research program to identify drugs to treat hepatitis C infection. Using our internal drug discovery capabilities and our proprietary HepDirect and NuMimetic technologies, we intend to discover and develop new drug compounds for the treatment of metabolic diseases, cancer 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 to treat 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 Sankyo is responsible for conducting clinical trials, but we have retained an option to co-promote CS-917 in North America, while with MB07133, we are solely responsible for development of the product candidate and have retained worldwide commercialization rights.

- *Establishing additional HepDirect partnerships.* Our proprietary HepDirect technology helps overcome some of the challenges faced in developing drugs for liver and metabolic diseases. We believe our HepDirect technology is broadly applicable to a wide variety of drug targets. We may partner this technology 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 are creating liver-targeting prodrugs of certain lead compounds that Merck is supplying to us. These compounds target the hepatitis C virus residing in the liver. This collaboration was recently extended and expanded.
- *Becoming a fully-integrated pharmaceutical company.* We plan to become a fully-integrated pharmaceutical company. In time and as resources allow, we will 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, CS-917 and pradefovir. In contrast, we have managed the early clinical development of MB07133 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.

#### *Sankyo*

In April 1997, we established a multi-year research, development and commercialization collaboration with 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 Sankyo. Sankyo has 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. Sankyo will have exclusive, worldwide commercialization rights to products developed under the agreement. 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 Sankyo and Metabasis oversees clinical development. Compounds that 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, Sankyo paid us license fees and sponsored research totaling \$20.25 million over the five-year discovery research portion of the collaboration and made an investment of \$7.25 million in our Series A preferred stock. As of December 31, 2004, 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 \$20.25 million in license fees and sponsored research, the \$7.25 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, Sankyo will pay us a royalty on net sales 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 Sankyo, under which Sankyo paid us a non-refundable \$8.5 million option fee that gave 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, Sankyo exercised its rights under the option agreement to designate an additional back-up compound, which 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. 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, 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, Sankyo has no rights to MB07803, and, should the hold currently on MB07803 be lifted, we may 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 Sankyo has no commercial or other rights to MB07803, the information that Metabasis receives regarding CS-917 has been reduced.

For a more detailed discussion, see the section in "Risk Factors" entitled "*We are dependent on our collaborations with Sankyo and Valeant for development of CS-917 and pradeфовir, respectively, and events involving these collaborations, our collaboration with Merck, or any future collaborations could prevent us from developing and commercializing our product candidates and achieving or sustaining profitability*" and, "*Conflicts may arise between us and any of our collaborators that could delay or prevent the development or commercialization of our product candidates.*"

In March 2005, we were notified by Sankyo that two serious adverse events involving lactic acidosis, a serious and potentially fatal condition, had occurred in a clinical trial evaluating the interaction of CS-917 with the marketed diabetes drug metformin. The serious adverse events were resolved after medical intervention. The two patients were administered CS-917 in combination with metformin. Three clinical trials that were ongoing at the time were stopped. Sankyo has informed us that one Phase I clinical trial of CS-917 is continuing and that one or more additional Phase I clinical trials may be initiated soon to further evaluate the product candidate. The continuing Phase I clinical trial does not combine CS-917 with metformin. In parallel with this activity, we and Sankyo, together

and separately, are evaluating the next steps, if any, to be taken in this program. In addition, we are evaluating the impact on our second generation treatment for diabetes, MB07803, which is believed to have the same therapeutic mechanism as CS-917.

The implications of these findings on our business could be significant. For a discussion of these implications, see the section in "Risk Factors" entitled "*Recent serious adverse events observed during a clinical trial of CS-917 may have a significant adverse impact on our business.*"

The term of our collaboration agreement, including the license of the additional back-up compound under our option agreement, will continue until all of 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 Sankyo if Sankyo does not diligently develop and market CS-917 in a particular country.

#### *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, 2004, 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.

*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 of \$1.4 million during the first year of the research term and is obligated to pay us an additional \$1.4 million of research funding in the second year of the research term. 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.

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.

*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 March 8, 2005, we owned a total of 24 issued U.S. patents, two allowed U.S. applications, 15 pending U.S. applications, and four pending U.S. provisional applications. In foreign countries, as of the same date, we owned a total of 66 issued patents, 22 allowed applications and 137 pending applications.

We co-own one of these pending U.S. applications, 19 of these foreign pending applications and two of these foreign allowed applications with Sankyo. As of the same date, we held rights to a total of two in-licensed U.S. patents.

We believe we have a strong intellectual property position, including 10 issued U.S. patents, two allowed U.S. applications, 19 pending U.S. applications, 52 foreign issued patents, 22 foreign allowed and 126 foreign pending applications that relate to proprietary technologies and compounds used in our current business. One patent that relates to proprietary technologies and compounds used in our current business expires in 2014. The remaining patents that relate to proprietary technologies and compounds used in our current business expire in 2018 through 2020. Fourteen of our issued U.S. patents relate to proprietary technologies and compounds that are no longer a primary focus of our business, and expire from 2009 through 2020. Our patent applications allowed or granted in foreign countries expire from 2006 through 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 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 worldwide commercialization rights to MB07133 and MB07803 as well as compounds from our other advanced research programs, with the exception of hepatitis C product candidates that are covered by our collaboration 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. Notwithstanding the recently reported serious adverse events related to CS-917, if it is ultimately determined safe and effective and approved for marketing, CS-917 may face significant competition from various formulations of metformin and products containing metformin. Metformin is a drug that, like CS-917, inhibits liver glucose production, albeit through an unknown mechanism. Because it does not cause weight gain, metformin is often prescribed as a first line therapy to obese diabetics, who are reported to comprise more than 90% of newly diagnosed type 2 diabetics. In addition, an inexpensive generic form of metformin recently became available. Accordingly, unless CS-917 demonstrates a significant benefit over metformin or demonstrates that it can be used in the patient population who do not tolerate and/or adequately respond to metformin treatment, the price required to effectively compete with the generic form of

metformin may be so low that it becomes uneconomical for us or Sankyo to market CS-917. As noted above, a recent clinical trial that combined CS-917 with metformin resulted in serious adverse events that are being further evaluated.

Other currently marketed oral drugs that may compete with CS-917 include:

- insulin sensitizers, including Actos (pioglitazone) and Avandia (rosiglitazone),
- sulfonylureas, including Glucotrol XL (glipizide),
- alpha glucosidase inhibitors, including Precose (acarbose), and
- prandial glucose regulators, including Starlix (nateglinide).

In addition, there is substantial ongoing discovery and development of novel treatments for type 2 diabetes, including late stage clinical development for glucagon-like peptide-1 (GLP-1) agonists, dipeptidyl peptidase IV (DPP-IV) inhibitors that enhance endogenous GLP-1 levels, and newer insulin sensitizers.

There are four currently approved treatments for hepatitis B in the U.S.:

- Intron A (interferon alfa-2b),
- Epivir-HBV and Zeffix (lamivudine),
- Hepsera (adefovir dipivoxil), and
- Baraclude (entecavir).

Pradefovir and Hepsera are prodrugs of the same active drug, and therefore will directly compete. In order to effectively compete with Hepsera, pradefovir will have to be significantly more beneficial or less expensive than Hepsera.

There are no currently approved drugs for primary liver cancer. Bayer Pharmaceuticals Corp. and Onyx Pharmaceuticals Inc. have begun a Phase III clinical trial of BAY-43-9006 (sorafenib) in patients with advanced liver cancer. Eximias is developing a product candidate called Thymitaq which is in Phase III clinical trials for the treatment of primary liver cancer. In addition, Amgen may be developing a product candidate called T67 which is in Phase II/III clinical trials for the treatment of primary liver cancer. We will also compete with non-surgical therapies that use either radioactive microscopic beads (such as TheraSpheres) or chemotherapy (known as Transcatheter Arterial Chemoembolization (TACE)) injected through a catheter directly into the liver.

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**

Sankyo and Valeant are responsible for all clinical and commercial manufacturing of CS-917 and pradefovir, respectively. We rely on several suppliers to produce sufficient quantities of MB07133 and MB07803 for use in 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*

CS-917, pradefovir, MB07133 and any other product candidates that we or our collaborators develop will require regulatory approval before they can be commercialized. Sankyo and Valeant are responsible for clinical development and regulatory approval of CS-917 and pradefovir, respectively, although we jointly oversee the clinical development of these product candidates through our participation in joint development committees. Although our collaboration with Merck has not yet yielded a product candidate, should it 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.

### *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 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 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 application 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,
- 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 a pre-approval inspection of the manufacturing facility to assess compliance with the FDA's current Good Manufacturing Practice, or CGMP, 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 measures of preliminary efficacy. Phase II usually involves studies designed to identify doses of the drug that result in suitable efficacy, safety and tolerance in patients with the targeted disease. Phase III clinical trials, commonly referred to as pivotal studies, are undertaken to further evaluate clinical efficacy and to test further for safety 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 FDA may deny approval of an NDA if applicable regulatory criteria are not satisfied, or if additional testing or information is required. Post-marketing testing, including Phase IV clinical trials, and surveillance to monitor the safety, efficacy and optimal use of a product may also be required, and the FDA may limit further marketing of the product based

on the results of post-market testing. FDA approval of any application may include 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 Services 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. Any failure to comply with these requirements may subject manufacturers to, among other things, fines and civil penalties, suspension or delay in product approval, product seizure or recall, or withdrawal of product approval.

With respect to post-market product advertising and promotion, the FDA imposes a number of complex regulations on entities that advertise and promote pharmaceutical drugs, which include, among others, standards for and regulations of 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 these regulations can result in penalties, including the issuance of a warning letter directing that deviations from FDA standards be corrected, total or partial suspension of production, and state and federal civil and criminal investigations and prosecutions.

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, 2004, we employed 88 full-time employees, consisting of 68 employees in research, development and regulatory affairs and 20 in management, administration, finance, receiving and facilities. As of the same date, 31 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.

### **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 SEC. 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.

### **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**

*Recent serious adverse events observed during a clinical trial of CS-917 may have a significant adverse impact on our business.*

The inhibition of gluconeogenesis can cause elevated levels of lactic acid, or lactate, which, if high and sustained, under certain conditions can lead to lactic acidosis, a serious and potentially fatal

condition. Certain pre-clinical trials have shown that CS-917 raises lactate levels two- to three-fold in some but not all animal models at glucose lowering doses. In a 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. The other six patients in this dose group as well as patients administered lower doses of CS-917 showed lactate levels within the normal range. In a 28-day Phase II clinical trial of CS-917, isolated instances of lactate elevation significantly above the normal range were seen in some patients in both CS-917 and placebo treated groups over the course of the 28 days. No patient exhibited sustained lactate levels significantly above the normal range over a period of consecutive days during the study. However, one patient who received 200 milligrams of CS-917 twice a day was withdrawn from the study by the investigator on day 15 due to concerns over consistently elevated lactate levels measured the previous day.

In March 2005, we were notified by Sankyo that two serious adverse events involving lactic acidosis, a serious and potentially fatal condition, had occurred in a clinical trial evaluating the interaction of CS-917 with the marketed diabetes drug metformin. The serious adverse events were resolved after medical intervention. The two patients were administered CS-917 in combination with metformin. Three clinical trials that were ongoing at the time were stopped. Sankyo has informed us that one Phase I clinical trial of CS-917 is continuing and that one or more additional Phase I clinical trials may be initiated soon to further evaluate the product candidate. The continuing Phase I clinical trial does not combine CS-917 with metformin. In parallel with this activity, we and Sankyo, together and separately, are evaluating the next steps, if any, to be taken in this program. In addition, we are evaluating the impact on our second generation treatment for diabetes, MB07803, which is believed to have the same therapeutic mechanism as CS-917.

It is also possible that CS-917 may cause other side effects. In certain pre-clinical studies, as expected based on the mechanism of the compound, 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 and/or decreasing other glucose-producing mechanisms in the body, 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 either the 14-day or 28-day clinical trials described above. Other side effects observed during early clinical trials of CS-917 included nausea and vomiting.

CS-917 currently is our most advanced product candidate and together with MB07803 represent a significant part of our clinical and advanced preclinical product pipeline. These findings could continue to interrupt, delay or halt clinical trials of both products 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. Our announcement of these findings has had a significant negative impact on our stock price. Our stock price could further decline when the implications of these findings are known.

These findings may have other significant adverse implications for our business, for example:

- We may be unable to obtain additional financing on acceptable terms, if at all,
- Sankyo may ultimately terminate development of CS-917 and may further decide not to develop a backup product candidate,

- Were our agreement with Sankyo to terminate we may determine not to further develop CS-917 and may not be able to establish a collaboration for its further development on acceptable terms, if at all,
- Were our agreement with Sankyo to terminate we may be unable to develop CS-917 further on our own due to resource constraints,
- We may determine not to further develop MB07803 and may not be able to establish a collaboration for its further development on acceptable terms, if at all,
- Even if development continues on CS-917 and MB07803 and these product candidates receive regulatory approval, these 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.

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

We have expended significant time, money and effort in the development of our three current product candidates, CS-917, pradelevir and MB07133. To date, clinical trials with CS-917 have demonstrated it was capable of significantly lowering blood glucose levels in type 2 diabetics, although three clinical studies of CS-917 were recently halted due to serious adverse events described above. Likewise, clinical trials conducted to date in patients treated with pradelevir have provided indications of efficacy. However, our product candidates will require additional development, clinical trials and regulatory clearances before they can be commercialized. Positive results from pre-clinical studies and early clinical trials do not necessarily mean later clinical trials will succeed. Before we can market these product candidates or MB07133, we will need to demonstrate that they are safe and effective in humans, and we will also need to obtain necessary marketing approval from the FDA, or similar foreign regulatory agencies. Our product development efforts may not lead to commercial drugs, either because our product candidates fail to be safe and effective in clinical trials or because we have inadequate financial or other resources to pursue our product candidates through the clinical trial process. If any of our product candidates fail to demonstrate safety or efficacy at any time or during any phase of development, we would experience potentially significant delays in, or be required to abandon, development of the product candidate. For instance, as noted above, a recent clinical trial that combined CS-917 with metformin resulted in serious adverse events that are being further evaluated and may lead to delays or abandonment of the project.

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

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

To receive regulatory approval for the commercialization of CS-917, pradelevir, MB07133 or any other product candidates that we may develop, adequate and well-controlled clinical trials must be

conducted to demonstrate safety and efficacy in humans to the satisfaction of the FDA in the U.S. and other regulatory agencies elsewhere in the world. In order to support marketing approval, these agencies typically require successful results in one or more Phase III clinical trials, which our current product candidates have not yet reached and may never reach. Clinical testing is expensive, can take many years and has an uncertain outcome. Failure can occur at any stage of the testing. We may experience numerous unforeseen events during, or as a result of, the clinical trial process that could delay or prevent commercialization of our current or future product candidates, including the following:

- our clinical trials may produce negative or inconclusive results,
- patient recruitment and enrollment in our clinical trials may be slower than we anticipate,
- costs of our clinical trials may be greater than we anticipate,
- our product candidates may cause undesirable side effects (such as those recently observed in a clinical trial of CS-917) 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. Companies frequently suffer significant setbacks in advanced clinical trials, even after earlier clinical trials have shown promising results. For instance, as noted above, a recent clinical trial that combined CS-917 with metformin resulted in serious adverse events that are being further evaluated and may lead to delays or abandonment of the project. Our clinical experience with our product candidates is limited, and to date we have conducted tests in less than the number of patients that will likely need to be studied to gain regulatory approval of these product candidates. The data collected from clinical trials with larger patient populations may not demonstrate sufficient safety and efficacy to support regulatory approval of these product candidates.

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

***Our product candidates may cause undesirable side effects that could delay or prevent their regulatory approval or commercialization.***

Three clinical trials involving our product candidate CS-917 were recently halted due to two serious adverse events that occurred in a clinical trial combining CS-917 with the marketed diabetes drug metformin. These findings could have significant adverse implications for our business. For a discussion of these implications, see the section in "Risk Factors" entitled "*Recent serious adverse events observed during a clinical trial of CS-917 may have a significant adverse impact on our business.*"

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. To date, clinical trials of both pradefovir and MB07133 have not demonstrated any byproduct-related toxicities. 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.

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

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

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

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

We have entered into collaborations with Sankyo and Valeant for the development and commercialization of CS-917 and pradefovir, respectively. We have also entered into a collaboration with Merck to seek new products for the treatment of hepatitis C infection. Sankyo and Valeant have agreed to finance the clinical trials for these product candidates and, if they are approved, manufacture and market them. Accordingly, we are dependent on Sankyo and Valeant to gain FDA and other foreign regulatory agency approval of, and to commercialize, CS-917 and pradefovir. Although our collaboration with Merck has not yet yielded a product candidate, should it be successful, we will be dependent on Merck for further development and commercialization of any resulting product candidate. Also, since we do not currently possess the resources necessary to independently develop and commercialize all of the potential products that may be based upon our technologies, including MB07133, we may need to enter into additional collaborative agreements to assist in the development and commercialization of some of these potential products. However, our discussions with potential collaborators may not lead to the establishment of new collaborations on acceptable terms, if at all.

We have limited control over the amount and timing of resources that Sankyo, Valeant, Merck or any future collaborators devote to our programs or potential products. These collaborators may breach or terminate their agreements with us or otherwise fail to conduct their collaborative activities successfully and in a timely manner. Further, our collaborators may not develop products that arise out of our collaborative arrangements or devote sufficient resources to the development, manufacture, marketing or sale of these products. In the event that one of our collaborations is terminated, and we

believe that the continued development or commercialization of a product candidate or drug compound covered by the collaboration is warranted, we would seek to obtain rights to develop and commercialize the product candidate or drug compound, if we did not already have those rights. We would then determine whether to continue the development or commercialization of the product candidate or drug compound independently or together with a new collaborator. However, in the event that we do not have sufficient resources to independently develop or commercialize the product candidate or drug compound, and we cannot establish a new collaboration on acceptable terms, we would be forced to discontinue its development or commercialization.

Our agreement with Sankyo contains certain rights and restrictions regarding our access to and use of confidential data and information generated by Sankyo. We have been developing MB07803, a second generation gluconeogenesis inhibitor that Sankyo has no rights to and that may be a direct competitor to CS-917. We have placed further development of MB07803 on hold pending the outcome of our evaluation of the recently reported serious adverse events that occurred in a recent clinical trial of CS-917. Because of this competitive situation and with our consent, the transfer of confidential information and data related to CS-917 from Sankyo has already been reduced and we expect that further reductions in information flow will occur. This situation may limit our ability to provide information regarding clinical results unless they are publicly released by Sankyo, may limit our ability to influence decisions made at Sankyo regarding CS-917, may limit our ability to accurately track Sankyo's diligence on the development program and could lead to disagreements between Sankyo and us.

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 collaboration with Merck involves Merck's proprietary compounds, if Merck terminates development of product candidates applying our HepDirect and other liver-targeting technology to those compounds, we may not have the right to pursue development of these product candidates on our own.***

The objective of our collaboration with Merck is to discover product candidates for the treatment of hepatitis C by applying our technology to certain Merck compounds. Accordingly, if Merck

terminates our collaboration before a defined stage of development of a product candidate, which it may do without cause at any time after the end of the collaboration's research term upon 90 days' advance written notice to us, we will not have any right to develop or commercialize that product candidate. In addition, if our 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.

Merck has an exclusive option for a specified period following the effective date of our agreement to license compounds resulting from our internal hepatitis C program. Consequently, if Merck terminates our collaboration, we may be at a significant disadvantage to our competitors in the research and development of treatments for hepatitis C as a result of having agreed to this restriction on our internal efforts.

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

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

- unwillingness on the part of a collaborator to pay us research funding, milestone payments or royalties we believe are due to us under our collaboration agreement,
- uncertainty regarding ownership of intellectual property rights arising from our collaborative activities, which could prevent us from entering into additional collaborations, or disagreements with our collaborators regarding the protection of intellectual property rights,
- unwillingness on the part of a collaborator to keep us informed regarding the progress of its development and commercialization activities or to permit public disclosure of the results of those activities, or
- slowing or cessation of a collaborator's development or commercialization efforts with respect to our product candidates.

Our agreement with Sankyo contains certain rights and restrictions regarding our access to and use of confidential data and information generated by Sankyo. We may develop MB07803, a second generation gluconeogenesis inhibitor that Sankyo has no rights to and that may be a direct competitor to CS-917. We have placed further development of MB07803 on hold pending the outcome of our evaluation of the recently reported serious adverse events that occurred in a recent clinical trial of CS-917. Because of this competitive situation and with our consent, the transfer of confidential information and data related to CS-917 from Sankyo has already been reduced and we expect that further reductions in information flow will occur. This situation may limit our ability to provide information regarding clinical results unless they are publicly released by Sankyo, may limit our ability to influence decisions made at Sankyo regarding CS-917, may limit our ability to accurately track Sankyo's diligence on the development program and could lead to disagreements between Sankyo and us.

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

We intend to use our proprietary technologies and our knowledge and expertise to discover, develop and commercialize new products for the treatment of metabolic diseases, cancer and certain other diseases linked to 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 be effective or safe for their designated use, which would prevent their advancement into clinical trials and impede our ability to maintain or expand our clinical development pipeline. Our ability to identify new drug compounds and advance them into clinical development also depends upon our ability to fund our research and development operations, and we cannot be certain that additional funding will be available on acceptable terms, or at all.

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

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

- obtaining regulatory approval to commence a clinical trial,
- reaching agreement on acceptable terms with prospective contract research organizations and trial sites,
- manufacturing sufficient quantities of a product candidate,
- obtaining institutional review board approval to conduct a clinical trial at a prospective site, and
- recruiting and enrolling patients to participate in a clinical trial.

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

- failure to conduct the clinical trial in accordance with regulatory requirements or clinical protocols,
- inspection of the clinical trial operations or trial site by the FDA or other regulatory authorities resulting in the imposition of a clinical hold,
- unforeseen safety issues such as the serious adverse events recently observed in a clinical trial of CS-917, or
- lack of adequate funding to continue the clinical trial.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

- issue warning letters,
- impose civil or criminal penalties,
- suspend regulatory approval,
- suspend any ongoing clinical trials,
- refuse to approve pending applications or supplements to approved applications filed by us or our collaborators,
- impose restrictions on operations, including costly new manufacturing requirements, or
- seize or detain products or require a product recall.

In order to market any products outside of the U.S., we and our collaborators must establish and comply with numerous and varying regulatory requirements of other countries regarding safety and efficacy. Approval procedures vary among countries and can involve additional product testing and additional administrative review periods. The time required to obtain approval in other countries might differ from that required to obtain FDA approval. The regulatory approval process in other countries may include all of the risks regarding FDA approval in the U.S. Regulatory approval in one country does not ensure regulatory approval in another, but a failure or delay in obtaining regulatory approval in one country may negatively impact the regulatory process in others. Failure to obtain regulatory approval in other countries or any delay or setback in obtaining such approval could have the same

adverse impact regarding FDA approval in the U.S., including the risk that our product candidates may not be approved for all indications requested, which could limit the uses of our product candidates and adversely impact potential royalties and product sales, and that such approval may be subject to limitations on the indicated uses for which the product may be marketed or require costly, post-marketing follow-up studies.

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

***Our inability to complete required renovations and improvements to our new facility in a timely fashion could increase our costs, interrupt continuing operations and delay or prevent the commercialization of our products.***

We perform all of our research, development, management, administrative and other activities in a single facility, which we currently occupy under a sublease from Sicor. The term of the sublease expires in September 2005, and may expire earlier if the master lease for the facility is terminated. We do not have a contractual option to renew the sublease and we have no control over the early termination of the master lease. In December 2004, we entered into a new lease for laboratory and office space in San Diego. This new facility will require extensive renovations and improvements to be ready for our occupancy by our scheduled move in date in September 2005. These renovations are being financed and constructed by our new landlord. Any delay in the completion of these renovations beyond the scheduled move in date could increase our costs, interrupt continuing operations and delay or prevent the commercialization of our products and adversely affect our ability to generate revenues, which could prevent us from achieving or maintaining profitability. For example, should any potential delay extend for several months or longer, we could be subject to eviction and/or litigation related to our inability to vacate our current facility at the end of our sublease term.

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

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

We are aware of many competitive products currently marketed or under development that are used to treat some of the diseases we have targeted. Notwithstanding the recently reported serious adverse events related to CS-917, if it is ultimately determined safe and effective and approved for marketing, CS-917 will face significant competition from various formulations of metformin and products containing metformin. Metformin is a drug that, like CS-917, inhibits liver glucose production, albeit through an unknown mechanism. Because it does not cause weight gain, metformin is often prescribed as a first line therapy to obese diabetics, who are reported to comprise more than 90% of newly diagnosed type 2 diabetics. Bristol-Myers-Squibb also markets Glucovance®, a single pill that contains both metformin and the insulin secretion enhancer glyburide. In addition, a less expensive generic form of metformin recently became available. Accordingly, unless CS-917 demonstrates a significant benefit over metformin or demonstrates that it can be used in the patient population who do not tolerate and/or adequately respond to metformin treatment, the price required to effectively compete with the generic form of metformin may be so low that it becomes uneconomical for us or Sankyo to market CS-917. As noted above, a recent clinical trial that combined CS-917 with metformin resulted in serious adverse events that are being further evaluated. Other competitors to CS-917 may

include, but are not limited to, the insulin sensitizers Actos® (pioglitazone), co-marketed by Takeda Chemical Industries, Ltd. and Eli Lilly and Company, Avandia® (rosiglitazone), marketed by GlaxoSmithKline PLC, and other products that may be developed from time to time. GlaxoSmithKline has combined metformin and Avandia in a single pill called Avandamet®.

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

There are no currently approved drugs for primary liver cancer. However, there are potential competitors and treatments which may include, but are not limited to: Bayer Pharmaceuticals Corp. and Onyx Pharmaceuticals Inc. which have begun a Phase III clinical trial of BAY-43-9006 (sorafenib) in patients with advanced liver cancer; Amgen Inc., which may be developing a product candidate called T67 currently in Phase II/III trials for the treatment of primary liver cancer; Eximias Pharmaceutical Corporation which is developing a product candidate called Thymitaq® currently in Phase III trials for the treatment of primary liver cancer and other products that may be developed from time to time. We will also compete with non-surgical therapies that use either radioactive microscopic beads (such as TheraSpheres) or chemotherapy (known as Transcatheter Arterial Chemoembolization (TACE)) injected through a catheter directly into the liver.

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

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

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

Our ability to develop and commercialize our products depends in part on our ability to manufacture, or arrange for collaborators or other third parties to manufacture, our products at a competitive cost, in accordance with regulatory requirements and in sufficient quantities for clinical testing and eventual commercialization. Sankyo and Valeant are responsible for all clinical and commercial manufacturing of CS-917 and pradefovir, respectively. We have relied on a number of suppliers to manufacture sufficient quantities of MB07133 for use in our current clinical trial. Although none of our current product candidates has been manufactured on a commercial scale our historical suppliers have manufactured other companies' products on a commercial scale. However, we have not

yet determined if our suppliers are capable of manufacturing our products on a commercial scale. Similarly, we rely on outside manufacturing for MB07803. We, our collaborators and third-party manufacturers may encounter difficulties with the small- and large-scale formulation and manufacturing processes required to manufacture our product candidates, resulting in delays in our clinical trials and regulatory submissions, in the commercialization of our product candidates or, if any of our product candidates is approved, in the recall or withdrawal of the product from the market. Further, development of large-scale manufacturing processes may require additional validation studies, which the FDA and other foreign regulatory agencies must review and approve. Our inability to enter into or maintain agreements with collaborators or capable third-party manufacturers on acceptable terms could delay or prevent the commercialization of our products, which would adversely affect our ability to generate revenues and could prevent us from achieving or maintaining profitability.

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

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

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

We do not have a sales and marketing organization, and we have no experience as a company in the sales, marketing and distribution of pharmaceutical products. Sankyo and Valeant are responsible for worldwide marketing and commercialization for CS-917 and pradefovir, respectively, although we have an option to co-promote CS-917 in North America with Sankyo. Although our collaboration with Merck has not yet yielded a product candidate, should it be successful, Merck will be responsible for worldwide marketing and commercialization of any resulting product candidate. In order to co-promote CS-917 in North America, or commercialize MB07133 or any future product candidates, we must develop our sales, marketing and distribution capabilities or make arrangements with a third party to perform these services. Developing a sales force is expensive and time consuming and could delay any product launch. We may be unable to establish and manage an effective sales force in a timely or cost-effective manner, if at all, and any sales force we do establish may not be capable of generating sufficient demand for our product candidates. To the extent that we enter into arrangements with

collaborators or other third parties to perform sales and marketing services, our product revenues are likely to be lower than if we directly marketed and sold our product candidates. If we are unable to establish adequate sales and marketing capabilities, independently or with others, we may not be able to generate significant revenues and may not become profitable.

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

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

- our ability to provide acceptable evidence of safety and efficacy,
- relative convenience and ease of administration,
- the prevalence and severity of any adverse side effects, such as the serious adverse events recently observed in a clinical trial of CS-917,
- availability of alternative treatments,
- pricing and cost effectiveness,
- effectiveness of our or our partners' sales and marketing strategy, and
- our ability to obtain sufficient third-party coverage or reimbursement.

If approved, CS-917 may have to be administered several times daily. Additionally, it may result in variable drug levels in different patient populations, which could complicate its use and limit its marketability. Since CS-917 is eliminated from the body through the kidney, it may be of limited use in diabetics with kidney dysfunction. Also, CS-917 and HepDirect prodrugs such as pradefovir and MB07133 may also exhibit interactions with other marketed drugs that could limit their combination with those drugs. Serious adverse events recently observed in a clinical trial of CS-917 in combination with metformin have led Sankyo to discontinue or review certain clinical trials and have raised questions about the safety of the potential use of CS-917 and metformin in combination. The inability to combine CS-917 with metformin may limit the marketability of the drug even if it is approved. In addition, primarily because the number of treatable patients in the U.S. with primary liver cancer is relatively small, we expect to market MB07133, if approved, at a relatively high price in the U.S. in order to generate sufficient revenues to recoup our costs and provide a return on our investment. This could prevent us from achieving market acceptance of MB07133 in the U.S. The number of treatable patients outside of the U.S. is much larger than the number of treatable patients in the U.S. However, because third party reimbursement in many of these countries is uncertain, we may be unable to recoup our costs or generate sufficient returns on our investment in these countries. If any of our product candidates is approved but does not achieve an adequate level of acceptance by physicians, healthcare payors and patients, we may not generate sufficient revenue from this product candidate and we may not become or remain profitable.

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

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

- our ability to set a price we believe is fair for our products,
- our ability to generate revenues and achieve or maintain profitability,

- the future revenues and profitability of our potential customers, suppliers and collaborators, and
- the availability of capital.

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

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

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

Since we became an independent company in 1999, we have increased the number of our full-time employees from 50 to 88 as of December 31, 2004. We may need to continue to expand our managerial, operational, financial and other resources in order to manage and fund our operations and clinical trials, continue our research and development and collaborative activities, and commercialize our product candidates. It is possible that our management and scientific personnel, systems and facilities currently in place may not be adequate to support this future growth. Our need to effectively manage our operations, growth and various projects requires that we continue to improve our operational, financial and management controls, reporting systems and procedures and to attract and retain sufficient numbers of talented employees. We may be unable to successfully implement these tasks on a larger scale and, accordingly, may not achieve our research, development and commercialization goals.

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

Our success depends on our continued ability to attract, retain and motivate highly qualified management and scientific personnel. The loss of the services of any principal member of our management or scientific staff, particularly Paul K. Laikind, Ph.D., our Chairman of the Board, Chief Executive Officer and President, and Mark D. Erion, Ph.D., our Executive Vice President of Research and Development, could delay or prevent the commercialization of our product candidates. We employ these individuals on an "at-will" basis and their employment can be terminated by us or them at any time, for any reason and with or without notice, subject to the terms of their stock restriction agreements and severance agreements.

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

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

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

An important part of our business strategy is to continue to develop a broad pipeline of product candidates. In addition to our internal drug development efforts, we may seek to expand our product pipeline, at the appropriate time and as resources allow, by acquiring products or businesses or in-licensing technologies that we believe are a strategic fit with our business and complement our existing product candidates and research programs. We are not currently a party to any agreements or commitments and we have no understandings with respect to any such acquisitions. Future acquisitions, however, may entail numerous operational and financial risks including:

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

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

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

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

We have incurred net losses from our inception. As of December 31, 2004, we had an accumulated deficit of approximately \$51.4 million. We expect to increase our operating expenses over the next several years as we continue and expand our research and development activities, including conducting clinical trials for our product candidates and further developing our product pipeline, acquiring or in-licensing products, technologies or businesses, and funding other working capital and general corporate purposes. As a result, we expect to continue to incur significant and increasing operating

losses for the foreseeable future. Because of the numerous risks and uncertainties associated with our product development efforts, we are unable to predict the extent of any future losses or when we will become profitable, if at all.

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

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

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

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

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

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

- the rate of progress and cost of our clinical trials and other research and development activities,
- the scope, prioritization and number of clinical development and research programs we pursue,
- the costs of expanding our operations, including costs related to our relocation to our new facility in 2005,
- the terms and timing of any collaborative, licensing and other arrangements that we may establish,
- the costs of filing, prosecuting, defending and enforcing any patent claims and other intellectual property rights,
- the costs and timing of regulatory approvals,
- the costs of establishing or contracting for sales and marketing capabilities,
- the effect of competing technological and market developments, and
- the extent to which we acquire or in-license new products, technologies or businesses.

Until we can generate significant continuing revenues, if ever, we expect to satisfy our future cash needs through public or private equity offerings, debt financings or corporate collaboration and licensing arrangements, as well as through interest income earned on cash balances. We cannot be certain that additional funding will be available on acceptable terms, or at all. The recent serious

adverse events that occurred in a clinical trial of CS-917 and their implications for the further development of CS-917 and MB07803 could adversely impact our future financing efforts. If adequate funds are not available, we may be required to delay, reduce the scope of or eliminate one or more of our research and development programs or our commercialization efforts and we may be unable to continue as a going concern.

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

We may raise additional funds through public or private equity offerings, debt financings or corporate collaboration and licensing arrangements. To the extent that we raise additional capital by issuing equity securities, our existing stockholders' ownership will be diluted. Any debt financing we enter into may involve covenants that restrict our operations. These restrictive covenants may include limitations on additional borrowing, specific restrictions on the use of our assets as well as prohibitions on our ability to create liens, pay dividends, redeem our stock or make investments. In addition, if we raise additional funds through collaboration and licensing arrangements, it may be necessary to relinquish potentially valuable rights to our potential products or proprietary technologies, or grant licenses on terms that are not favorable to us.

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

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

- the development status of our product candidates, including results of our clinical trials,
- our recommendation of additional drug compounds for clinical development,
- our addition or termination of research programs or funding support,
- variations in the level of expenses related to our product candidates or research programs, and
- our execution of collaborative, licensing or other arrangements, and the timing of payments we may make or receive under these arrangements.

For example, our announcement of serious adverse events recently observed in a clinical trial of CS-917 had a significant negative impact on our stock price. Quarterly fluctuations in our operating results may, in turn, cause the price of our stock to fluctuate substantially. We believe that quarterly comparisons of our financial results are not necessarily meaningful and should not be relied upon as an indication of our future performance.

### **Risks Related to our Intellectual Property**

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

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

The filing, prosecution and defense of patents at pharmaceutical and biotechnology companies can be highly uncertain and involve complex legal and factual questions for which important legal principles remain unresolved. No consistent policy regarding the breadth of claims allowed in biotechnology patents has emerged to date in the U.S. The biotechnology patent situation outside the U.S. is even

more uncertain. We may be particularly affected by this because we expect that pradefovir and MB07133, if approved, will be marketed in foreign countries with high incidences of hepatitis B and primary liver cancer, respectively. Decisions or actions regarding patent filing and/or changes in either the patent laws or in interpretations of patent laws in the U.S. and other countries may diminish the value of our intellectual property.

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

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

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

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

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

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

Our commercial success also depends upon our ability and the ability of our collaborators to develop, manufacture, market and sell our product candidates and use our proprietary technologies without infringing the proprietary rights of third parties. Numerous U.S. and foreign issued patents and pending patent applications, which are owned by third parties, exist in the fields in which we and our collaborators are developing products. Because patent applications can take many years to issue, there may be currently pending applications, unknown to us, which may later result in issued patents that our product candidates or proprietary technologies may infringe. We have not conducted a complete search of existing patents to identify existing patents that our product candidates or proprietary technologies may inadvertently infringe.

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

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

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

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

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

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

We are aware of third party patents and patent applications in European and other foreign countries with claims to prodrugs of adefovir. These patents are scheduled to expire in September 2011. Although we do not believe that any valid claim covers pradevovir, we cannot guarantee this. If it is determined that patent claims are valid and cover pradevovir, we may not be able to commercialize pradevovir in foreign countries, including those in Europe. Further, we are aware that a patent term extension of one of these prodrug patents has been requested in one or more European countries based on the regulatory approval of Hepsera. If the extension request is granted, the patents would expire in September 2016. If granted, this extension may have an adverse impact on the commercialization of pradevovir in any such country if it is determined that the patent claims are valid and cover pradevovir. Additional third party patents covering Hepsera or adefovir may exist, and may expire later than April 2006 in the U.S. and later than 2011 in foreign countries.

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

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

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

The radioactive isotopes and compounds we use can cause radiation contamination to our facility. State and federal laws require that before permanently leaving a facility in which radioactive materials have been used, the user of the radioactive materials must make certain that the facility passes a series of tests known as decommissioning. The decommissioning process is highly regulated and may be expensive. In connection with the upcoming expiration of our current sublease and our planned move to a new facility, we have incurred, and will continue to incur, costs in the decommissioning of our current facility. We cannot predict the ultimate amount of these costs, and they may be substantial. The decommissioning process may also prevent us from moving to an alternate facility in a timely manner, which could increase our costs and delay or prevent the commercialization of our products.

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

We face an inherent risk of product liability exposure related to the testing of our product candidates in human clinical trials, and will face an even greater risk if we sell our product candidates commercially. An individual may bring a liability claim against us if one of our product candidates causes, or merely appears to have caused, an injury. If we cannot successfully defend ourselves against the product liability claim, we will incur substantial liabilities. Regardless of merit or eventual outcome, liability claims may result in:

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

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

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

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

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

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

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

- changes in the regulatory status of our product candidates, including the status and results of our clinical trials,
- events affecting Sankyo, Valeant, Merck or any future collaborators,

- announcements of new products or technologies, commercial relationships or other events by us or our competitors,
- regulatory developments in the U.S. and foreign countries,
- fluctuations in stock market prices and trading volumes of similar companies,
- variations in our quarterly operating results,
- changes in securities analysts' estimates of our financial performance,
- changes in accounting principles,
- sales of large blocks of our common stock, including sales by our executive officers, directors and significant stockholders,
- additions or departures of key personnel, and
- discussion of us or our stock price by the financial and scientific press and in online investor communities.

For example, our announcement of serious adverse events recently observed in a clinical trial of CS-917 had a significant negative impact on our stock price. Our stock price could further decline when the implications of these findings are known.

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

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

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

Changes in the laws and regulations affecting public companies, including the provisions of the Sarbanes-Oxley Act of 2002 and rules adopted or proposed by the Securities and Exchange Commission and by the Nasdaq Stock Market, will result in increased costs to us as we continue to evaluate the implications of these laws and regulations and respond to their requirements. These laws and regulations could make it more difficult or more costly for us to obtain certain types of insurance, including director and officer liability insurance, and we may be forced to accept reduced policy limits and coverage or incur substantially higher costs to obtain the same or similar coverage. The impact of these events could also make it more difficult for us to attract and retain qualified persons to serve on our board of directors, our board committees or as executive officers. We are presently evaluating and

monitoring developments with respect to these laws and regulations and cannot predict or estimate the amount or timing of additional costs we may incur to respond to their requirements.

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

Our executive officers, directors and holders of 5% or more of our outstanding common stock, beneficially owned approximately 73% of our common stock as of December 31, 2004. As a result, these stockholders, acting together, are able to control all matters requiring approval by our stockholders, including the election of directors and the approval of mergers or other business combination transactions. The interests of this group of stockholders may not always coincide with our interests or the interests of other stockholders, and they may act in a manner that advances their best interests and not necessarily those of other stockholders.

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

Our current stockholders hold a substantial number of shares of our common stock that they are, or will be able to sell in the public market in the near future. In addition, we have outstanding warrants to purchase 1,347,176 shares of common stock that, if exercised, will result in these additional shares becoming available for sale. A large portion of these shares and warrants are held by a small number of persons and investment funds. Sales by these stockholders or warrant holders of a substantial number of shares could significantly reduce the market price of our common stock. Moreover, the holders of 11,043,949 shares of unregistered common stock and warrants to purchase 1,347,176 shares of unregistered common stock have rights, subject to some conditions, to require us to file registration statements covering the unregistered shares they currently hold or may acquire upon exercise of the warrants, or to include these shares in registration statements that we may file for ourselves or other stockholders.

## **Item 2. Properties**

We sublease approximately 44,000 square feet of space in San Diego, California under a sublease agreement with Sidor dated September 2000. We perform all of our research, development, management, administrative and other activities in this facility. The term of the sublease expires in September 2005, and may expire earlier if the master lease for the facility is terminated. We do not have a contractual option to renew the sublease and we have no control over the early termination of the master lease.

On December 21, 2004, we entered into a new lease agreement pursuant to which we will lease up to approximately 82,000 square feet of real estate space in San Diego, California consisting of laboratory and office space. The lease commences on the later of September 1, 2005, or the date that certain landlord-funded tenant improvements are satisfactorily completed, and has an initial term of 10 years unless extended or sooner terminated. We have options to extend the lease for two renewal periods of five years each.

We believe that our facilities are adequate for our current needs.

## **Item 3. Legal Proceedings**

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

## **Item 4. Submission of Matters to a Vote of Security Holders**

Not applicable.

## PART II

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

#### Market Information

Our common stock has been traded on the Nasdaq National Market since June 16, 2004 under the symbol MBRX. Prior to such time, there was no public market for our common stock. The following table sets forth the high and low sales prices for our common stock as reported on the Nasdaq National Market for the periods indicated.

	<u>High</u>	<u>Low</u>
<b>Year Ended December 31, 2004</b>		
Second Quarter (beginning June 16, 2004) .....	\$7.13	\$5.75
Third Quarter .....	\$6.95	\$5.15
Fourth Quarter .....	\$7.25	\$5.11

As of March 1, 2005, there were approximately 121 holders of record of our common stock.

#### Dividend Policy

We have never declared or paid cash dividends on our capital stock. We currently intend to retain all available funds and any future earnings for use in the operation and expansion of our business and do not anticipate paying any cash dividends in the foreseeable future.

#### Recent Sales of Unregistered Securities and Use of Proceeds

For the year ended December 31, 2004, during the period prior to our initial public offering, we issued and sold 251,301 shares of our common stock that were not registered under the Securities Act of 1933, as amended, to our employees upon the exercise of options for aggregate cash consideration of \$311,566. During the same period, we granted options to our employees and non-employee directors to purchase 270,208 shares of common stock at a weighted average exercise price of \$3.15 per share. No underwriters were involved in the foregoing stock or option issuances. The issuance of these securities prior to our initial public offering was exempt from registration under the Securities Act of 1933, as amended, in reliance on Rule 701 promulgated under the Securities Act of 1933, as amended, as transactions by an issuer under compensatory benefit plans and contracts relating to compensation within the parameters required by Rule 701. Following the closing of our initial public offering, these securities were issued pursuant to a registration statement on Form S-8 that we filed with the Securities and Exchange Commission.

Our initial public offering of our common stock, par value \$0.001, was effected through a Registration Statement on Form S-1 (File No. 333-112437) that was declared effective by the Securities and Exchange Commission on June 15, 2004. The Registration Statement covered the offer and sale of up to 5,750,000 shares of our common stock for an aggregate offering price of \$40.3 million. Our initial public offering commenced on June 15, 2004. On June 21, 2004, 5,000,000 shares of our common stock were sold for an aggregate offering price of \$35.0 million. On July 20, 2004, 75,000 shares of our common stock were sold for an aggregate offering price of \$525,000 upon the partial exercise of the underwriters' over-allotment option. Our initial public offering terminated following the sale of all of the securities registered on the registration statement and the expiration of the underwriters' over-allotment option. Our initial public offering resulted in aggregate proceeds to us of approximately \$31.1 million, net of underwriting discounts and commissions of approximately \$2.5 million and offering expenses of approximately \$1.9 million, through a syndicate of underwriters managed by SG Cowen &

Co., LLC, Deutsche Bank Securities Inc., Thomas Weisel Partners LLC, and Legg Mason Wood Walker, Incorporated.

No offering expenses were paid directly or indirectly to any of our directors or officers (or their associates) or person owning ten percent or more of any class of our equity securities or to any other affiliates. All offering expenses were paid directly to others.

As of December 31, 2004, we had used approximately \$31.1 million of the initial public offering proceeds for investments in medium-term, interest-bearing obligations, investment-grade instruments, or guaranteed obligations of the U.S. government.

The foregoing payments were direct payments made to third parties who were not our directors or officers (or their associates), persons owning ten percent or more of any class of our equity securities or any other affiliate, except that the proceeds used for working capital included regular compensation for officers and directors. The use of proceeds does not represent a material change from the use of proceeds described in the prospectus we filed pursuant to Rule 424(b)(4) of the Securities Act of 1933, as amended, with the Securities and Exchange Commission on June 16, 2004.

#### **Equity Compensation Plan Information**

The information required to be disclosed by Item 201(d) of Regulation S-K, "Securities Authorized for Issuance Under Equity Compensation Plans," is incorporated by reference to Item 12 of Part III of this Form 10-K.

## Item 6. Selected Financial Data

The statement of operations data and balance sheet data presented below should be read in conjunction with Item 7, Management's Discussion and Analysis of Financial Condition and Results of Operations, and the financial statements and related notes appearing elsewhere in this Form 10-K.

	Years Ended December 31,				
	2004	2003	2002	2001	2000
	(In thousands, except per share amounts)				
<b>Statements of Operations Data:</b>					
Revenue	\$ 6,837	\$ 9,124	\$ 2,278	\$ 7,664	\$ 3,653
Operating expenses:					
Research and development	16,675	15,048	12,609	9,464	7,659
General and administrative	3,804	2,955	2,531	2,131	1,451
Amortization of employee stock-based compensation(1)	1,633	504	23	—	—
Total operating expenses	22,112	18,507	15,163	11,595	9,110
Loss from operations	(15,275)	(9,383)	(12,885)	(3,931)	(5,457)
Other income (expense), net	303	(46)	88	249	265
Net loss(2)	(14,972)	(9,429)	(12,797)	(3,682)	(5,192)
Preferred stock deemed dividend(3)	—	(24,900)	—	—	—
Net loss attributable to common stockholders	<u>\$(14,972)</u>	<u>\$(34,329)</u>	<u>\$(12,797)</u>	<u>\$(3,682)</u>	<u>\$(5,192)</u>
Basic and diluted net loss per share:(2)					
Historical	<u>\$ (1.49)</u>	<u>\$ (23.84)</u>	<u>\$ (10.12)</u>	<u>\$ (4.44)</u>	<u>\$ (13.04)</u>
Pro forma	<u>\$ (0.98)</u>	<u>\$ (3.74)</u>			
Shares used to compute basic and diluted net loss per share:(2)					
Historical	<u>10,034</u>	<u>1,440</u>	<u>1,265</u>	<u>830</u>	<u>398</u>
Pro forma	<u>15,254</u>	<u>9,187</u>			

- (1) The amortization of employee stock-based compensation is composed of \$1,138,000 and \$358,000 related to research and development activities and \$495,000 and \$146,000 related to general and administrative activities for the years ended December 31, 2004 and 2003, respectively.
- (2) Please see Note 1 to our financial statements for an explanation of the method used to calculate the historical and pro forma net loss per share and the number of shares used in the computation of the per share amounts.
- (3) As disclosed in Note 7 to our financial statements, we recorded a deemed dividend in connection with the issuance of our Series E preferred stock.

	As of December 31,				
	2004	2003	2002	2001	2000
	(In thousands)				
<b>Balance Sheet Data:</b>					
Cash, cash equivalents and securities available-for-sale	\$ 43,855	\$ 25,257	\$ 19,562	\$ 25,572	\$ 12,439
Working capital	40,906	22,342	13,693	24,539	10,349
Total assets	47,860	29,110	21,733	28,438	13,800
Long-term obligations (including current portion)	2,226	1,820	2,854	3,907	3,154
Accumulated deficit	(51,365)	(36,393)	(26,964)	(14,167)	(10,485)
Total stockholders' equity	41,864	23,437	8,756	21,475	5,947

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

You should read the following discussion and analysis together with our audited financial statements and the notes to those statements included elsewhere in this annual report on Form 10-K. This discussion contains forward-looking statements that involve risks and uncertainties. See "Forward-Looking Statements" in Part I, Item 1 of this annual report on Form 10-K.

### Overview

We are a biopharmaceutical company focused on the discovery, development and commercialization of novel small molecule drugs principally to treat metabolic diseases, cancer and certain other diseases linked to pathways in the liver. Examples of common metabolic diseases include diabetes, hyperlipidemia, a disease involving elevated levels of lipids such as cholesterol, and obesity. We have established a broad and growing product pipeline targeting large markets with significant unmet medical needs.

We currently have three product candidates in clinical development, CS-917, pradevovir and MB07133, indicated for the treatment of type 2 diabetes, hepatitis B and primary liver cancer, respectively. Recently, three clinical trials of CS-917 were halted due to two serious adverse events that occurred in a clinical trial combining CS-917 with the marketed diabetes treatment metformin. We and Sankyo, together and separately, are evaluating the next steps, if any, to be taken in this program. CS-917 was in Phase II clinical trials at the time the serious adverse events occurred. In addition to our product candidates in clinical development, we have research programs focused on metabolic diseases linked to pathways in the liver such as type 2 diabetes, hyperlipidemia and obesity, as well as liver diseases such as hepatitis C and liver fibrosis. We believe our advanced research programs, which are research programs in which we have identified lead drug compounds and shown them to have efficacy in animal models, have the potential to yield additional clinical development candidates within the next two years. One of these advanced research programs yielded a compound, MB07803, that we recommended for clinical development in the first quarter of 2004. MB07803 is a clinical development candidate for the treatment of type 2 diabetes that works by the same mechanism as CS-917. Continuing preclinical development of MB07803 is currently on hold pending the outcome of our evaluation of the recently reported serious adverse events related to CS-917.

These findings could have significant adverse implications for our business. For a discussion of these implications, see the section in "Risk Factors" entitled "*Recent serious adverse events observed during a clinical trial of CS-917 may have a significant adverse impact on our business.*"

We have incurred annual net losses since inception. As of December 31, 2004, our accumulated deficit was approximately \$51.4 million. We expect to incur substantial and increasing losses for the next several years as we:

- continue to develop current and future clinical development candidates,
- commercialize our product candidates, if any, that receive regulatory approval,
- continue and expand our research and development programs, and
- acquire or in-license products, technologies or businesses that are complementary to our own.

We have a limited history of operations and, to date, we have not generated any product revenues. In addition to our initial public offering in June 2004, we have financed our operations and internal growth through private placements of preferred stock as well as direct payments of sponsored research funding, license fees, milestone payments and equity investments from our collaborative partners. We have received additional funding through equipment financing arrangements and Small Business Innovation Research, or SBIR, grants.

Our agreements with collaborators may include joint marketing or promotion arrangements of our products or products licensed from our collaborators. For example, we have retained co-promotion rights for CS-917 in North America. Alternatively, we may grant exclusive marketing rights to our collaborators in exchange for up-front fees, milestones and royalties on future sales, if any. We have licensed worldwide commercialization rights for pradeфовir to Valeant. We have retained worldwide commercialization rights to MB07133, MB07803 and all of the compounds generated from our current research programs, with the exception of hepatitis C product candidates covered by our collaboration with Merck. We intend to eventually market one or more of the product candidates for which we retain commercialization rights through our own sales force or with a co-promotion partner in the U.S. and through strategic collaborations abroad.

We will rely on our partners or third-party manufacturers to produce sufficient quantities of these products for pre-clinical and clinical studies and large-scale commercialization upon their approval.

Our business is subject to significant risks, including the risks inherent in our ongoing clinical trials and the regulatory review and approval process, the results of our research and development efforts, reliance on third parties for the development and commercialization of our product candidates, competition from other products and uncertainties associated with obtaining and enforcing patent rights.

### **Research and Development**

Our research and development expenses consist primarily of compensation and other expenses for research and development personnel, costs associated with pre-clinical development and clinical trials of our product candidates, facility costs, supplies and materials, costs for consultants and related contract research and depreciation. We charge all research and development expenses to operations as they are incurred.

Our research and development activities are primarily focused on the clinical trial of MB07133, the potential further advanced pre-clinical development of MB07803, and the research and development of the lead compounds in our other research programs. In September 2003, we initiated a Phase I clinical trial of MB07133 in the U.S. and Asia. We are responsible for all costs incurred in our research programs with the exception of the hepatitis C program partnered with Merck. Under the terms of our collaboration agreement with Merck, we had received approximately \$1.4 million in research funding through December 31, 2004. Sankyo and Valeant are responsible for the costs of clinical development of CS-917 and pradeфовir, respectively.

At this time, due to the risks inherent in the clinical trial process and given the early stage of development of our product candidates and lead compounds from our research programs, we are unable to estimate with any certainty the costs we will incur in the continued development of our product candidates for commercialization. Due to these same factors, we are unable to determine the anticipated completion dates for our current research and development projects. However, we expect our research and development costs to be substantial and to increase as we continue the development of our current product candidates, as well as continue and expand our research programs.

Generally, Phase I clinical trials can be expected to last from 6 to 18 months, Phase II clinical trials can be expected to last from 12 to 24 months and Phase III clinical trials can be expected to last from 18 to 36 months. However, clinical development timelines vary widely, as do the likelihood of success and total costs of clinical trials. Although we are currently focused primarily on advancing MB07133 and potentially, MB07803, through clinical development, we anticipate that we will make determinations as to which research and development projects to pursue and how much funding to direct to each project on an ongoing basis in response to the scientific and clinical success of each product candidate, as well as an ongoing assessment of its market potential.

The lengthy process of seeking regulatory approvals for our product candidates, and the compliance with applicable regulations, require the expenditure of substantial resources. Any failure by us to obtain, or any delay in obtaining, regulatory approvals could cause our research and development expenditures to increase and, in turn, have a material unfavorable effect on our results of operations. We cannot be certain when any net cash inflow due to sales of any of our current product candidates will commence.

### **General and Administrative**

General and administrative expenses consist primarily of salaries and other related costs for personnel in executive, finance, accounting, business development and human resource functions. Other costs include facility costs not otherwise included in research and development expenses and professional fees for legal and accounting services.

We anticipate continued increases in general and administrative expenses for investor relations and other activities associated with operating as a publicly-traded company. These increases will also likely include the hiring of additional personnel.

### **Other Income, Net**

Other income, net includes interest earned on our cash, cash equivalents and securities available-for-sale, net of interest expense.

### **Critical Accounting Policies**

Our discussion and analysis of our financial condition and results of operations are based on our audited financial statements, which have been prepared in accordance with U.S. generally accepted accounting principles, or GAAP. The preparation of these financial statements requires us to make estimates and judgments that affect the reported amounts of assets, liabilities, revenues and expenses and related disclosure of contingent assets and liabilities. We review our estimates on an on-going basis. We base our estimates on historical experience and on various other assumptions that we believe to be reasonable under the circumstances, the results of which form the basis for making judgments about the carrying values of assets and liabilities. Actual results may differ from these estimates under different assumptions or conditions. We believe the following accounting policies to be critical to the judgments and estimates used in the preparation of our financial statements.

*Revenue Recognition.* Our revenue recognition policies are in accordance with Securities and Exchange Commission Staff Accounting Bulletin, or SAB, 101, *Revenue Recognition in Financial Statements*, as amended by SAB 104, *Revenue Recognition*, and Emerging Issues Task Force, or EITF, Issue 00-21, *Revenue Arrangements with Multiple Deliverables*. Our agreements generally contain multiple elements, including downstream milestones and royalties. All fees are nonrefundable. Revenue from milestones is recognized when earned, provided that:

- the milestone event is substantive and its achievability was not reasonably assured at the inception of the agreement, and
- collaborator funding, if any, of our performance obligations after the milestone achievement will continue at a level comparable to before the milestone achievement.

If both of these criteria are not met, the milestone payment is recognized over the remaining minimum period of our performance obligations under the agreement. Upfront, nonrefundable fees under our collaborations are recognized over the period the related services are provided. Nonrefundable upfront fees not associated with our future performance are recognized when received. Amounts received for research funding are recognized as revenues as the services are performed. Amounts received for research funding for a specific number of full-time researchers are recognized as

revenue as the services are provided, as long as the amounts received are not refundable regardless of the results of the research project.

*Clinical Trial Expenses.* Our clinical trials are often conducted under contracts with multiple research institutions and clinical research organizations that conduct and manage clinical trials on our behalf. The financial terms of these agreements are subject to negotiation and vary from contract to contract and may result in uneven payment flows. Generally, these agreements set forth the scope of work to be performed at a fixed fee or unit price. Payments under the contracts depend on factors such as the successful enrollment of patients or the completion of clinical trial milestones. Expenses related to clinical trials generally are accrued based on contracted amounts applied to the actual level of patient enrollment and activity according to the protocol. Other incidental costs related to patient enrollment are accrued when known. If contracted amounts are modified based upon changes in the clinical trial protocol or scope of work to be performed, we modify our accruals accordingly on a prospective basis.

### **Recently Issued Accounting Pronouncements**

In December 2004, the Financial Accounting Standards Board, or FASB issued SFAS No. 123R, *Share Based Payment*. This statement is a revision to SFAS 123 and supersedes Accounting Principles Board, or APB Opinion No. 25 and amends FASB Statement No. 95, *Statement of Cash Flows*. This statement requires a public entity to expense the cost of employee services received in exchange for an award of equity instruments. This statement also provides guidance on valuing and expensing these awards, as well as disclosure requirements of these equity arrangements. This statement is effective for the first interim reporting period that begins after June 15, 2005.

SFAS 123R permits public companies to choose between the following two adoption methods:

1. A “modified prospective” method in which compensation cost is recognized beginning with the effective date (a) based on the requirements of SFAS 123R for all share-based payments granted after the effective date and (b) based on the requirements of Statement 123 for all awards granted to employees prior to the effective date of SFAS 123R that remain unvested on the effective date, or
2. A “modified retrospective” method which includes the requirements of the modified prospective method described above, but also permits entities to restate based on the amounts previously recognized under SFAS 123 for purposes of pro forma disclosures either (a) all prior periods presented or (b) prior interim periods of the year of adoption.

As permitted by SFAS 123, we currently account for share-based payments to employees using APB Opinion No. 25’s intrinsic value method and, as such, we generally recognize no compensation cost for employee stock options. The impact of the adoption of SFAS 123R cannot be predicted at this time because it will depend on levels of share-based payments granted in the future. However, valuation of employee stock options under SFAS 123R is similar to SFAS 123, with minor exceptions. For information about what our reported results of operations and earnings per share would have been had we adopted SFAS 123, please see the discussion under the heading “Stock Based Compensation” in Note 1 to our audited financial statements included elsewhere in this annual report on Form 10-K. Accordingly, the adoption of SFAS 123R’s fair value method will have a significant impact on our results of operations, although it will have no impact on our overall financial position. SFAS 123R also requires the benefits of tax deductions in excess of recognized compensation cost to be reported as a financing cash flow, rather than as an operating cash flow as required under current literature. This requirement will reduce net operating cash flows and increase net financing cash flows in periods after adoption. Due to timing of the release of SFAS 123R, we have not yet completed the analysis of the ultimate impact that this new pronouncement will have on our results of operations, nor the method of adoption for this new standard.

In March 2004, the FASB issued EITF 03-1, *The Meaning of Other-Than-Temporary Impairment and Its Application to Certain Investments*. EITF 03-1, which was originally effective for interim and annual reporting periods beginning after June 15, 2004 requires a three-step model to determine other-than-temporary impairments for all current and future investments in marketable securities. In September 2004, the FASB delayed the requirement to record impairment losses under EITF 03-1 until new guidance is issued. We do not expect that the adoption of EITF 03-1 will have a material impact on our operating results and financial position.

## **Results of Operations**

### *Comparison of the Years Ended December 31, 2003 and 2004*

**Revenues.** Revenues were \$9.1 million for the year ended December 31, 2003, compared with \$6.8 million for the year ended December 31, 2004. The \$2.3 million decrease was mainly due to a decline in license fee revenue of approximately \$7.2 million which was attributable to a one-time payment associated with an exclusive option agreement with Sankyo that expired in 2003. This decrease was partially offset by higher milestone revenue in the current year period, which included \$3.5 million earned under our collaboration agreement with Sankyo. Additionally, we realized a \$1.4 million increase in sponsored research resulting from the initiation in 2004 of the research portion of our collaboration agreement with Merck.

**Research and Development Expenses.** Research and development expenses were \$15.0 million for the year ended December 31, 2003, compared with \$16.7 million for the year ended December 31, 2004. The \$1.7 million increase was mainly due to increased spending of \$720,000 in payroll and related benefits as a result of a higher average number of employees in 2004, a \$551,000 increase in pre-clinical development expense for MB07803 and a \$442,000 increase in clinical trials expenses related to MB07133.

**General and Administrative Expenses.** General and administrative expenses were \$3.0 million for the year ended December 31, 2003, compared with \$3.8 million for the year ended December 31, 2004. The \$800,000 increase reflected mainly an increase in professional services expense of \$407,000 and higher payroll and related benefits costs of \$369,000 as a result of a higher average number of employees in 2004.

**Amortization of Employee Stock-based Compensation.** In connection with the grant of stock options to employees and directors, we recorded amortization of deferred stock-based compensation of approximately \$504,000 and \$1.6 million for the years ended December 31, 2003 and 2004, respectively. As of December 31, 2004, we had approximately \$4.9 million of deferred stock-based compensation. We anticipate recording amortization of deferred compensation expense related to stock option grants of approximately \$1.8 million, \$1.7 million, \$1.3 million and \$128,000 for the years ended December 31, 2005, 2006, 2007 and 2008, respectively.

In 2003, our board of directors authorized a transaction, effective June 30, 2003, calling for three of our executive officers to agree to tender 487,702 shares of their previously vested common stock and subject them to a new monthly vesting schedule over a four-year period commencing on June 30, 2003. This transaction was entered into as repayment for outstanding principal and accrued interest on loans we made to those executive officers in connection with their purchase of our common stock in June 1999. We recorded \$711,000 of deferred compensation at June 30, 2003, to be amortized over the four-year vesting period of the underlying common stock. We recorded amortization of deferred compensation of approximately \$89,000 and \$178,000 for the years ended December 31, 2003 and 2004, respectively. We anticipate recording amortization of deferred compensation expense related to the new vesting of previously vested shares tendered by our executive officers of approximately \$178,000, \$178,000 and \$88,000 for the periods ended December 31, 2005, 2006 and 2007, respectively.

*Other Income, Net.* Net interest expense was \$46,000 for the year ended December 31, 2003, compared to net interest income of \$303,000 for the year ended December 31, 2004. The \$349,000 net increase was mainly due to higher invested cash resulting from the proceeds of our initial public offering in June 2004.

*Comparison of the Years Ended December 31, 2002 and 2003*

*Revenues.* Revenues were \$2.3 million for the year ended December 31, 2002, compared with \$9.1 million for the year ended December 31, 2003. The \$6.8 million increase was primarily the result of increased license fee revenue of \$6.7 million in 2003 from an exclusive option agreement we entered into in October 2002 with Sankyo, plus a \$1.0 million clinical development milestone we earned under our collaboration agreement with Valeant in the second quarter of 2003. The increase was offset by a decline of \$1.2 million in 2003 in sponsored research resulting from the completion of the research portion of our collaboration agreement with Sankyo in April 2002.

*Research and Development Expenses.* Research and development expenses were \$12.6 million for the year ended December 31, 2002, compared with \$15.0 million for the year ended December 31, 2003. The \$2.4 million increase was primarily due to increased spending of \$1.2 million in salaries and benefits and \$153,000 increase in lab supply expenditures associated with an overall increase in staffing levels of nine employees in 2003 as our internal programs continued to progress plus a \$1.0 million increase for external contracted research primarily related to MB07133.

*General and Administrative Expenses.* General and administrative expenses were \$2.5 million for the year ended December 31, 2002 compared with \$3.0 million for the year ended December 31, 2003. The \$424,000 increase was primarily due to the salary and benefit expenses related to hiring our Vice President of Business Development in May 2002 plus the amortization of deferred compensation resulting from the loan payments on tendered shares made by Mr. Beck and Dr. Laikind in June 2003.

*Amortization of Employee Stock-based Compensation.* In connection with the grant of stock options to employees and directors, we recorded deferred stock-based compensation of approximately \$261,000 and \$5.2 million during the years ended December 31, 2002 and 2003, respectively. We recorded amortization of deferred stock-based compensation of approximately \$23,000 and \$504,000 for the years ended December 31, 2002 and 2003, respectively. As of December 31, 2003, we had approximately \$4.9 million of deferred stock-based compensation.

In 2003, our board of directors authorized a transaction, effective June 30, 2003, calling for three of our executive officers to agree to tender 487,702 shares of their previously vested common stock and subject them to a new monthly vesting schedule over a four-year period commencing on June 30, 2003. This transaction was entered into as repayment for outstanding principal and accrued interest on loans we made to those executive officers in connection with their purchase of our common stock in June 1999 of \$514,000 and related taxes paid on their behalf by us. As part of this transaction, we made aggregate income tax payments of \$249,000 on behalf of our executive officers for estimated income taxes incurred in connection with this transaction, \$197,000 of which was satisfied by us through the application of the value of the shares tendered to us. The amount of shares tendered was based upon the then fair value for the common stock as determined by our board of directors. In April 2004, the compensation committee of our board of directors determined the actual income taxes incurred by our executive officers in connection with this transaction and, as a result, authorized us to make additional aggregate income tax payments of \$57,000 on their behalf and directly reimburse these officers an aggregate amount of \$78,000 for income tax payments made by them. We recorded \$711,000 of deferred compensation at June 30, 2003, to be amortized over the four-year vesting period of the underlying common stock. We recorded amortization of deferred compensation of approximately \$89,000 for the year ended December 31, 2003. There was no deferred compensation recorded in the year ended December 31, 2002.

*Other Income, Net.* Interest income was \$378,000 for the year ended December 31, 2002, compared with \$177,000 for the year ended December 31, 2003, a decrease of \$201,000. The decrease was due to lower average cash and investment balances and lower prevailing interest rates during 2003. Interest expense was \$295,000 for the year ended December 31, 2002, compared with \$226,000 for the year ended December 31, 2003, a decrease of \$69,000. The decrease was primarily due to the lowering of our outstanding debt balances as a result of our prepayment in October 2002 of \$2.0 million of principal and accrued interest on a convertible term loan.

### **Liquidity and Capital Resources**

On June 21, 2004, we completed an initial closing of our initial public offering in which we sold 5,000,000 shares of common stock for proceeds of \$30.6 million, net of underwriting discounts and commissions and offering expenses. In addition, on July 20, 2004, we completed an additional closing of our initial public offering in which we sold an additional 75,000 shares of common stock pursuant to the exercise by the underwriters of an over-allotment option which resulted in proceeds of \$0.5 million, net of underwriting discounts and commissions. Prior to our initial public offering, we financed our operations and internal growth primarily through private placements of preferred stock as well as direct payments of sponsored research funding, license fees, milestone payments and equity investments from our collaborative partners. Additional funding has come through equipment financing arrangements and via our receipt of SBIR grant funds.

As of December 31, 2004, we had financed through leases and loans the purchase of equipment and leasehold improvements totaling approximately \$4.2 million, of which \$2.2 million was outstanding at that date. The loans are collateralized with the purchased equipment, bear interest at rates ranging from approximately 8.6% to 12.1%, and are due in monthly installments through December 2008. Additionally, we have received cumulative SBIR grant funding of approximately \$1.2 million through December 31, 2004.

As of December 31, 2004, we had \$43.9 million in cash and cash equivalents and securities available-for-sale as compared to \$25.3 million as of December 31, 2003, an increase of \$18.6 million. The increase mainly reflected net proceeds of \$31.1 million raised following our initial public offering in June 2004, partially offset by net cash used in operations of \$12.6 million due largely to our net operating loss of \$15.0 million. Net cash used in investing activities of \$20.1 million for the year ended December 31, 2004 resulted from net purchases of investments of \$18.7 million and \$1.3 million of equipment purchases. Net cash provided by financing activities was \$32.5 million primarily reflecting \$31.1 million in net proceeds raised from our initial public offering.

As of December 31, 2003, we had \$25.3 million in cash and cash equivalents and securities available-for-sale as compared to \$19.6 million as of December 31, 2002, an increase of \$5.7 million. This increase resulted primarily from the proceeds from the sale of \$24.9 million of Series E preferred stock in October 2003 partially offset from our operating loss and principal payments on loans. Net cash used in operating activities amounted to \$15.7 million for the year ended December 31, 2003, primarily reflecting the net loss for this period of \$9.4 million plus \$7.2 million due to the amortization of deferred revenue related to the Sankyo option fee, offset by non-cash charges for depreciation and amortization of \$564,000 and amortization of deferred employee stock-based compensation of \$504,000. Net cash used in investing activities of \$7.7 million for the year ended December 31, 2003 resulted from net purchases of short-term investments of \$6.8 million and \$898,000 of equipment purchases. Net cash provided by financing activities was \$22.3 million for the year ended December 31, 2003, primarily reflecting \$23.8 million in net proceeds from the sale of Series E preferred stock and \$864,000 from equipment loans offset by our principal payments on notes payable and capital leases of \$1.9 million and the prepayment of offering costs of \$430,000.

The following summarizes our long-term contractual obligations as of December 31, 2004:

<u>Contractual Obligations</u>	<u>Total</u>	<u>Payments Due by Period</u>			
		<u>Less than 1 Year</u>	<u>1 to 3 Years</u>	<u>4 to 5 Years</u>	<u>After 5 Years</u>
Operating leases . . . . .	\$28,911	\$1,353	\$3,489	\$5,222	\$18,847
Capital leases . . . . .	67	16	32	19	—
Equipment financing . . . . .	2,500	1,006	1,312	182	—
Other contractual obligations . . . . .	200	50	50	50	50
Total . . . . .	<u>\$31,678</u>	<u>\$2,425</u>	<u>\$4,883</u>	<u>\$5,473</u>	<u>\$18,897</u>

We also enter into agreements with clinical sites and contract research organizations for the conduct of our clinical trials. We will make payments to these sites and organizations based upon the number of patients enrolled and the length of their participation in the clinical trials. As of December 31, 2004, we had made payments of \$821,000 to clinical sites or contract research organizations in connection with our Phase I clinical trial for MB07133. At this time, due to the variability associated with these agreements, we are unable to estimate with certainty the future patient enrollment costs we will incur.

Our future capital uses and requirements depend on numerous forward-looking factors. These factors may include but are not limited to the following:

- the rate of progress and cost of our clinical trials and other research and development activities,
- the scope, prioritization and number of clinical development and research programs we pursue,
- the costs of expanding our operations, including costs related to our relocation to our new facility in 2005,
- the terms and timing of any collaborative, licensing and other arrangements that we may establish,
- the costs of filing, prosecuting, defending and enforcing any patent claims and other intellectual property rights,
- the costs and timing of regulatory approvals,
- the costs of establishing or contracting for manufacturing, sales and marketing capabilities,
- the effect of competing technological and market developments, and
- the extent to which we acquire or in-license new products, technologies or businesses.

In January 2005, Merck extended the research portion of our collaboration for an additional year through December 2005. This extension will provide an additional \$1.4 million of sponsored research funding in 2005.

We believe that our existing cash, cash equivalents and short-term investments will be sufficient to meet our projected operating requirements through at least the next twelve months.

Until we can generate significant cash from our operations, we expect to continue to fund our operations with existing cash resources that were primarily generated from the proceeds of offerings of our equity securities, cash payments under our strategic collaborations, debt financing arrangements and government grants. In addition, we may finance future cash needs through the sale of other equity securities, entering into additional strategic collaboration agreements, government grants and debt financing. However, we may not be successful in obtaining additional collaboration agreements, or in receiving milestone or royalty payments under current or future agreements. In addition, we cannot be

sure that our existing cash, cash equivalents and short-term investments resources will be adequate or that additional financing will be available when needed or that, if available, financing will be obtained on terms favorable to us or our stockholders. Having insufficient funds may require us to delay, scale back or eliminate some or all of our research or development programs or to relinquish greater or all rights to product candidates at an earlier stage of development or on less favorable terms than we would otherwise choose. Failure to obtain adequate financing also may adversely affect our ability to operate as a going concern. If we raise additional funds by issuing equity securities, substantial dilution to existing stockholders would likely result. If we raise additional funds by incurring debt financing, the terms of the debt may involve significant cash payment obligations as well as covenants and specific financial ratios that may restrict our ability to operate our business.

As of December 31, 2004, we did not have any relationships with unconsolidated entities or financial partnerships, such as entities often referred to as structured finance or special purpose entities, which would have been established for the purpose of facilitating off-balance sheet arrangements or other contractually narrow or limited purposes. In addition, we do not engage in trading activities involving non-exchange traded contracts. As such, we are not materially exposed to any financing, liquidity, market or credit risk that could arise if we had engaged in these relationships.

#### **Related Party Transactions**

For a description of our related party transactions, see Item 13 of Part III of this Form 10-K, "Certain Relationships and Related Transactions."

#### **Item 7A. Quantitative and Qualitative Disclosures About Market Risk**

Our primary exposure to market risk is interest income sensitivity, which is affected by changes in the general level of U.S. interest rates, particularly because the majority of our investments are in short-term marketable securities. Due to the nature of our short-term investments, we believe that we are not subject to any material market risk exposure. We do not have any foreign currency or other derivative financial instruments.

Our long-term capital lease obligations bears interest at fixed rates and therefore we do not have significant market risk exposure with respect to these obligations.

#### **Item 8. Financial Statements and Supplementary Data**

The information required to be disclosed herein is incorporated by reference to Item 15 of Part III of this Form 10-K.

#### **Item 9. Changes in and Disagreements with Accountants on Accounting and Financial Disclosures**

Not applicable.

#### **Item 9A. Controls and Procedures**

We maintain disclosure controls and procedures that are designed to ensure that information required to be disclosed in our Exchange Act reports is recorded, processed, summarized and reported within the time periods specified in the Securities and Exchange Commission's rules and forms and that such information is accumulated and communicated to our management, including our chief executive officer and chief financial officer, as appropriate, to allow for timely decisions regarding required disclosure. In designing and evaluating the disclosure controls and procedures, management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving the desired control objectives, and management is required to apply its judgment in evaluating the cost-benefit relationship of possible controls and procedures.

As required by Securities and Exchange Commission Rule 13a-15(b), we carried out an evaluation, under the supervision and with the participation of our management, including our chief executive officer and chief financial officer, of the effectiveness of the design and operation of our disclosure controls and procedures as of the end of the period covered by this report. Based on the foregoing, our chief executive officer and chief financial officer concluded that our disclosure controls and procedures were effective at the reasonable assurance level.

There was no change in our internal control over financial reporting during the fourth fiscal quarter of the period covered by this report that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

**Item 9B. Other Information**

Not applicable.

### **PART III**

#### **Item 10. Directors and Executive Officers of the Registrant**

The information required by this item will be set forth in the sections entitled "Election of Directors", "Code of Business Conduct and Ethics", "Executive Officers" and "Section 16(a) Beneficial Ownership Reporting Compliance" in our definitive proxy statement to be filed with the Securities and Exchange Commission in connection with the Annual Meeting of our Stockholders (the "Proxy Statement"), which is expected to be filed not later than 120 days after the end of our fiscal year ended December 31, 2004, and is incorporated in this report by reference.

#### **Item 11. Executive Compensation**

The information required by this item will be set forth in the section entitled "Compensation of Executive Officers" in the Proxy Statement and is incorporated in this report by reference.

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

The information required by this item will be set forth in the sections entitled "Security Ownership of Certain Beneficial Owners and Management" and "Equity Compensation Plan Information" in the Proxy Statement and is incorporated in this report by reference.

#### **Item 13. Certain Relationships and Related Transactions**

The information required by this item will be set forth in the section entitled "Certain Relationships and Related Transactions" in the Proxy Statement and is incorporated in this report by reference.

#### **Item 14. Principal Accountant Fees and Services**

The information required by this item will be set forth in the section entitled "Ratification of Selection of Independent Auditors" in the Proxy Statement and is incorporated in this report by reference.

## PART IV

### Item 15. Exhibits and Financial Statement Schedules

- (a) The following documents are filed as part of this report:
- 1) The following financial statements of Metabasis Therapeutics, Inc. are included in this report beginning on page F-1 hereto:
    - Report of Independent Registered Public Accounting Firm
    - Balance sheets as of December 31, 2004 and 2003
    - Statements of operations for the years ended December 31, 2004, 2003 and 2002
    - Statements of stockholders' equity for the years ended December 31, 2004, 2003 and 2002
    - Statements of cash flows for the years ended December 31, 2004, 2003 and 2002
    - Notes to financial statements
  - 2) List of financial statement schedules. All financial statement schedules are omitted because they are not applicable or the required information is shown in the financial statements or notes thereto.
  - 3) List of exhibits required by Item 601 of Regulation S-K. See part (c) below.
- (c) Exhibits. The following exhibits are filed as a part of this report:

Exhibit Number	Description
2.1(1)	Asset and Liability Transfer Agreement dated December 17, 1997 between the Company and Gensia Sicor Inc.
2.2(1)	Master Agreement dated June 30, 1999 among the Company, Sicor Inc., Paul K. Laikind, Mark D. Erion and John W. Beck.
3.1(1)	Amended and Restated Certificate of Incorporation of the Company.
3.2(1)	Amended and Restated Bylaws of the Company.
4.1(1)	Form of Common Stock Certificate.
4.2(1)	Stock Purchase Warrant dated February 6, 2001 issued to GATX Ventures, Inc.
4.3(1)	Warrant to Purchase 26,000 Shares of Series C Preferred Stock dated February 6, 2001 issued to GATX Ventures, Inc., as amended July 26, 2001.
4.4(1)	Warrant to Purchase 19,000 Shares of Series C Preferred Stock dated July 26, 2001, issued to GATX Ventures, Inc.
4.5(1)	Warrant to Purchase 30,666 Shares of Series D Preferred Stock dated April 8, 2002, issued to GATX Ventures, Inc.
4.6(1)	Form of Stock Purchase Warrant issued to participants in the Company's Series C Preferred Stock financing dated July 18, 2000.
4.7(1)	Form of Stock Purchase Warrant issued to participants in the Company's Series D Preferred Stock financing dated October 18, 2001.

Exhibit Number	Description
4.8(1)	Form of letter agreement entered into between the Company and its warrant holders.
4.9(1)	Letter agreement dated October 18, 2001 entered into between the Company and Sprout Capital IX, L.P. and its affiliates.
4.10(1)	Series E Preferred Stock Purchase Agreement dated October 28, 2003 between the Company and certain of its stockholders.
4.11(1)	Amended and Restated Investors' Rights Agreement dated October 28, 2003 between the Company and certain of its stockholders.
10.1(1)+	Form of Indemnity Agreement.
10.2(1)+	Amended and Restated 2001 Equity Incentive Plan and Form of Stock Option Agreement thereunder.
10.3(1)+	2004 Non-Employee Directors' Stock Option Plan and Form of Stock Option Agreement thereunder.
10.4(1)+	2004 Employee Stock Purchase Plan and Form of Offering Document thereunder.
10.5(1)+	Employment offer letter dated March 17, 1998 between the Company and John W. Beck.
10.6(1)+	Employment offer letter dated March 31, 2002 between the Company and Edgardo Baracchini.
10.8(1)+	Stock Restriction Agreement dated June 30, 2003 between the Company and Paul K. Laikind.
10.9(1)+	Stock Restriction Agreement dated June 30, 2003 between the Company and Mark D. Erion.
10.10(1)+	Stock Restriction Agreement dated June 30, 2003 between the Company and John W. Beck.
10.11(1)+	Severance Agreement dated April 3, 2002 between the Company and Edgardo Baracchini.
10.12(1)+	Severance Agreement dated June 30, 2003 between the Company and Paul K. Laikind.
10.13(1)+	Severance Agreement dated June 30, 2003 between the Company and Mark D. Erion.
10.14(1)+	Severance Agreement dated June 30, 2003 between the Company and John W. Beck.
10.15(1)	License Agreement dated June 30, 1999 between the Company and Sicor Inc.
10.16(1)	Sublease Agreement dated September 1, 2000 between the Company and Sicor Inc.
10.17(1)*	Amended and Restated Collaborative Research and Development and License Agreement dated June 30, 1999 between the Company and Sankyo Company, Ltd., as amended February 9, 2000 and March 22, 2001.
10.18(1)*	Exclusive Option Agreement dated October 21, 2002 between the Company and Sankyo Company, Ltd.
10.19(2)	Development and License Agreement dated October 1, 2001 between the Company and Valeant Pharmaceuticals International.

Exhibit Number	Description
10.20(1)	Letter agreement dated March 8, 2002 among the Company, Valeant Pharmaceuticals International and Ribapharm Inc.
10.21(1)	Equipment Loan and Security Agreement daed February 6, 2001 between the Company and GATX Ventures, Inc., as amended July 26, 2001 and April 8, 2002.
10.22(1)	Master Security Agreement dated August 27, 2003 between the Company and Oxford Finance Corporation.
10.23(1)*	Exclusive License and Research Collaboration Agreement dated December 23, 2003 between the Company and Merck & Co., Inc.
10.24(3)	Amendment No. 1 to Sublease Agreement dated March 18, 2004 between the Company and Sicor Inc.
10.25(4)	Amendment No. 2 to Sublease Agreement dated September 14, 2004 between the Company and Sicor Inc.
10.26(5)	Lease Agreement dated December 21, 2004 between the Company and CarrAmerica Realty, L.P.
21.1(1)	Subsidiaries of the Company.
23.1	Consent of Independent Registered Public Accounting Firm.
31.1	Certification of Chief Executive Officer pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
31.2	Certification of Chief Financial Officer pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
32	Certifications of Chief Executive Officer and Chief Financial Officer pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.

+ Indicates management contract or compensatory plan.

\* Confidential treatment has been granted with respect to certain portions of this exhibit. Omitted portions have been filed separately with the Securities and Exchange Commission.

- (1) Incorporated by reference to the exhibit of the same number to the Company's Registration Statement on Form S-1 (No. 333-112437), originally filed on February 3, 2004.
- (2) Incorporated by reference to Exhibit 10.18 to the Registration Statement on Form S-1 (No. 333-39350), originally filed on June 15, 2000 by Ribapharm Inc., now a wholly-owned subsidiary of Valeant Pharmaceuticals International.
- (3) Incorporated by reference to Exhibit 10.1 to the Company's Quarterly Report on Form 10-Q for the quarterly period ended September 30, 2004.
- (4) Incorporated by reference to Exhibit 10.2 to the Company's Quarterly Report on Form 10-Q for the quarterly period ended September 30, 2004.
- (5) Incorporated by reference to Exhibit 99.1 to the Company's Current Report on Form 8-K filed on December 23, 2004.

## SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities and Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

METABASIS THERAPEUTICS, INC.

Dated: March 31, 2005

By: /s/ PAUL K. LAIKIND

Paul K. Laikind, Ph.D.  
*Chief Executive Officer and President*

Pursuant to the requirements of the Securities Exchange Act of 1934, this report has been signed below by the following persons on behalf of the registrant and in the capacities and on the dates indicated.

Signature	Title	Date
<u>/s/ PAUL K. LAIKIND</u> Paul K. Laikind, Ph.D.	Chairman of the Board, Chief Executive Officer, President and Secretary (Principal Executive Officer)	March 31, 2005
<u>/s/ JOHN W. BECK</u> John W. Beck, C.P.A.	Vice President of Finance, Chief Financial Officer and Treasurer (Principal Financial and Accounting Officer)	March 31, 2005
<u>/s/ DANIEL D. BURGESS</u> Daniel D. Burgess, M.B.A.	Director	March 31, 2005
<u>/s/ MARK D. ERION</u> Mark D. Erion, Ph.D.	Executive Vice President of Research and Development and Director	March 31, 2005
<u>/s/ LUKE B. EVNIN</u> Luke B. Evnin, Ph.D.	Director	March 31, 2005
<u>/s/ HEINZ W. GSCHWEND</u> Heinz W. Gschwend, Ph.D.	Director	March 31, 2005
<u>/s/ DAVID F. HALE</u> David F. Hale	Director	March 31, 2005
<u>/s/ ARNOLD L. ORONSKY</u> Arnold L. Oronsky, Ph.D.	Director	March 31, 2005
<u>/s/ WILLIAM R. ROHN</u> William R. Rohn	Director	March 31, 2005

**METABASIS THERAPEUTICS, INC.**  
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## REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

The Board of Directors and Stockholders of  
Metabasis Therapeutics, Inc.

We have audited the accompanying balance sheets of Metabasis Therapeutics, Inc. as of December 31, 2004 and 2003, and the related statements of operations, stockholders' equity and cash flows for each of the three years in the period ended December 31, 2004. These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on these financial statements based on our audits.

We conducted our audits in accordance with the standards of the Public Company Accounting Oversight Board (United States). Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement. We were not engaged to perform an audit of the Company's internal control over financial reporting. Our audit includes consideration of internal control over financial reporting as a basis for designing audit procedures that are appropriate in the circumstances, but not for the purpose of expressing an opinion on the effectiveness of the Company's internal control over financial reporting. Accordingly, we express no such opinion. An audit also includes examining, on a test basis, evidence supporting the amounts and disclosures in the financial statements, assessing the accounting principles used and significant estimates made by management, and evaluating the overall financial statement presentation. We believe that our audits provide a reasonable basis for our opinion.

In our opinion, the financial statements referred to above present fairly, in all material respects, the financial position of Metabasis Therapeutics, Inc. at December 31, 2004 and 2003 and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2004, in conformity with U.S. generally accepted accounting principles.

/s/ ERNST & YOUNG LLP

San Diego, California  
March 7, 2005

**METABASIS THERAPEUTICS, INC.**  
**BALANCE SHEETS**  
(in thousands, except par value data)

	December 31,	
	2004	2003
<b>Assets</b>		
Current assets:		
Cash and cash equivalents .....	\$ 10,921	\$ 11,017
Securities available-for-sale .....	32,934	14,240
Accounts receivable .....	525	957
Other current assets .....	1,126	466
Total current assets .....	45,506	26,680
Property and equipment, net .....	2,354	1,727
Prepaid offering costs .....	—	504
Other assets .....	—	199
Total assets .....	\$ 47,860	\$ 29,110
<b>Liabilities and stockholders' equity</b>		
Current liabilities:		
Accounts payable .....	\$ 864	\$ 767
Accrued liabilities .....	2,835	2,502
Deferred rent .....	67	—
Deferred revenue, current portion .....	—	458
Current portion of capital lease obligations, net of discount .....	834	611
Total current liabilities .....	4,600	4,338
Deferred rent .....	—	122
Other long-term liabilities .....	4	4
Capital lease obligations, net of current portion and discount .....	1,392	1,209
Stockholders' equity:		
Preferred stock, \$0.001 par value; 5,000 shares authorized:		
Convertible preferred stock, \$0.001 par value; 5,000 and 74,766 shares authorized at December 31, 2004 and December 31, 2003, respectively; 0 and 63,632 shares issued and outstanding at December 31, 2004 and December 31, 2003, respectively.	—	64
Common stock, \$0.001 par value; 100,000 and 129,840 shares authorized at December 31, 2004 and December 31, 2003, respectively; 18,169 and 1,773 shares issued and outstanding at December 31, 2004 and December 31, 2003, respectively.	18	2
Additional paid-in capital .....	98,602	65,255
Deferred compensation .....	(5,337)	(5,485)
Accumulated deficit .....	(51,365)	(36,393)
Accumulated other comprehensive loss .....	(54)	(6)
Total stockholders' equity .....	41,864	23,437
Total liabilities and stockholders' equity .....	\$ 47,860	\$ 29,110

*See accompanying notes.*

**METABASIS THERAPEUTICS, INC.**  
**STATEMENTS OF OPERATIONS**  
(in thousands, except per share data)

	Years Ended December 31,		
	2004	2003	2002
Revenues:			
Sponsored research . . . . .	\$ 1,375	\$ —	\$ 1,166
Milestones . . . . .	4,500	1,000	—
License fees . . . . .	458	7,631	911
Other revenue . . . . .	504	493	201
Total revenues . . . . .	<u>6,837</u>	<u>9,124</u>	<u>2,278</u>
Operating expenses:			
Research and development . . . . .	16,675	15,048	12,609
General and administrative . . . . .	3,804	2,955	2,531
Amortization of employee stock-based compensation . . . . .	1,633	504	23
Total operating expenses . . . . .	<u>22,112</u>	<u>18,507</u>	<u>15,163</u>
Loss from operations . . . . .	(15,275)	(9,383)	(12,885)
Other income (expense):			
Interest income . . . . .	531	177	378
Interest expense . . . . .	(228)	(226)	(295)
Other, net . . . . .	—	3	5
Total interest and other income (expense) . . . . .	<u>303</u>	<u>(46)</u>	<u>88</u>
Net loss . . . . .	\$(14,972)	\$(9,429)	\$(12,797)
Deemed dividend-beneficial conversion feature for Series E preferred stock . . . . .	—	(24,900)	—
Net loss applicable to common stockholders . . . . .	<u>(14,972)</u>	<u>(34,329)</u>	<u>(12,797)</u>
Basic and diluted net loss per share (1) . . . . .	<u>\$ (1.49)</u>	<u>\$(23.84)</u>	<u>\$ (10.12)</u>
Shares used to compute basic and diluted net loss per share (1) . . . . .	<u>10,034</u>	<u>1,440</u>	<u>1,265</u>
The composition of employee stock-based compensation is as follows:			
Research and development . . . . .	\$ 1,138	\$ 358	\$ 16
General and administrative . . . . .	495	146	7
	<u>\$ 1,633</u>	<u>\$ 504</u>	<u>\$ 23</u>

(1) As a result of the conversion of our preferred stock into 11.0 million shares of our common stock upon completion of our initial public offering on June 16, 2004, there is a lack of comparability in the basic and diluted net loss per share amounts for the periods presented above. Please reference Note 1 for an unaudited pro forma basic and diluted net loss per share calculation for the periods presented.

See accompanying notes.

**METABASIS THERAPEUTICS, INC.**  
**STATEMENTS OF STOCKHOLDERS' EQUITY**  
(in thousands)

	Convertible Preferred Stock		Common Stock		Additional Paid-In Capital	Deferred Compensation	Notes Receivable From Stockholders	Accumulated Deficit	Accumulated Other Comprehensive Income (Loss)	Total Stockholders' Equity (Deficit)
	Shares	Amount	Shares	Amount						
Balance at December 31, 2001	39,600	\$ 40	1,680	\$ 2	\$ 36,028	\$ —	\$(425)	\$(14,167)	\$ (3)	21,475
Net loss	—	—	—	—	—	—	—	(12,797)	—	(12,797)
Unrealized gain on short-term investments	—	—	—	—	—	—	—	—	4	4
Net comprehensive loss	—	—	—	—	—	—	—	—	—	(12,793)
Issuance of common stock for stock option exercises	—	—	26	—	27	—	—	—	—	27
Deferred employee stock-based compensation	—	—	—	—	261	(261)	—	—	—	—
Amortization of employee stock-based compensation	—	—	—	—	—	23	—	—	—	23
Issuance of preferred stock warrant as discount on equipment loan	—	—	—	—	22	—	—	—	—	22
Issuance of stock options for services	—	—	—	—	2	—	—	—	—	2
Balance at December 31, 2002	39,600	40	1,706	2	36,340	(238)	(425)	(26,964)	1	8,756
Net loss	—	—	—	—	—	—	—	(9,429)	—	(9,429)
Unrealized loss on short-term investments	—	—	—	—	—	—	—	—	(7)	(7)
Net comprehensive loss	—	—	—	—	—	—	—	—	—	(9,436)
Issuance of common stock for option exercises	—	—	67	—	45	—	—	—	—	45
Issuance of Series E preferred stock, net of offering costs of approximately \$1,137	24,032	24	—	—	23,739	—	—	—	—	23,763
Beneficial conversion feature for Series E preferred stock	—	—	—	—	24,900	—	—	—	—	24,900
Deemed dividend for Series E convertible preferred stock	—	—	—	—	(24,900)	—	—	—	—	(24,900)
Deferred employee stock-based compensation	—	—	—	—	5,209	(5,209)	—	—	—	—
Adjustment to deferred compensation for cancellation of options	—	—	—	—	(80)	80	—	—	—	—
Amortization of deferred employee stock-based compensation	—	—	—	—	—	504	—	—	—	504
Shares tendered in exchange for notes receivable from stockholders	—	—	—	—	—	—	425	—	—	425
Issuance of stock options for services	—	—	—	—	2	—	—	—	—	2
Deferred compensation from tendered shares subject to vesting	—	—	—	—	—	(711)	—	—	—	(711)
Amortization of deferred compensation from tendered shares subject to vesting	—	—	—	—	—	89	—	—	—	89
Balance at December 31, 2003	63,632	64	1,773	2	65,255	(5,485)	—	(36,393)	(6)	23,437
Net loss	—	—	—	—	—	—	—	(14,972)	—	(14,972)
Unrealized loss on short-term investments	—	—	—	—	—	—	—	—	(48)	(48)
Net comprehensive loss	—	—	—	—	—	—	—	—	—	(15,020)
Issuance of common stock in initial public offering and follow-on offering, net of offering costs of \$1,894	—	—	5,075	5	31,139	—	—	—	—	31,144
Conversion of convertible preferred stock into common stock	(63,632)	(64)	11,036	11	53	—	—	—	—	—
Issuance of common stock for option exercises	—	—	255	—	314	—	—	—	—	314
Issuance of common stock pursuant to the Employee Stock Purchase Plan	—	—	30	—	178	—	—	—	—	178
Deferred employee stock-based compensation	—	—	—	—	1,705	(1,705)	—	—	—	—
Adjustment to deferred compensation for cancellation of options	—	—	—	—	(42)	42	—	—	—	—
Amortization of deferred employee stock-based compensation	—	—	—	—	—	1,633	—	—	—	1,633
Amortization of deferred compensation from tendered shares subject to vesting	—	—	—	—	—	178	—	—	—	178
Balance at December 31, 2004	—	\$ —	18,169	\$ 18	\$ 98,602	\$(5,337)	\$ —	\$(51,365)	\$(54)	\$ 41,864

See accompanying notes.

**METABASIS THERAPEUTICS, INC.**  
**STATEMENTS OF CASH FLOWS**  
(in thousands)

	Years ended December 31,		
	2004	2003	2002
<b>Operating activities</b>			
Net loss	\$(14,972)	\$ (9,429)	\$(12,797)
Adjustments to reconcile net loss to net cash used in operating activities:			
Amortization of deferred employee stock-based compensation	1,633	504	23
Amortization of deferred compensation on tendered shares	178	89	—
Deferred rent	(55)	(10)	33
Depreciation and amortization	699	564	424
Amortization of discount on equipment loan	15	15	13
Stock options issued for services	—	2	2
Change in operating assets and liabilities:			
Accounts receivable	432	(778)	1,148
Other current assets	(660)	(205)	(28)
Other assets	199	50	(43)
Deferred revenue	(458)	(7,175)	4,723
Accounts payable	97	6	136
Accrued liabilities and other long-term liabilities	333	638	697
Net cash flows used in operating activities	<u>(12,559)</u>	<u>(15,729)</u>	<u>(5,669)</u>
<b>Investing activities</b>			
Purchases of securities available-for-sale	(40,327)	(15,215)	(11,630)
Sales/maturities of securities available-for-sale	21,585	8,450	9,900
Purchases of property and equipment	(1,326)	(898)	(806)
Net cash flows used in investing activities	<u>(20,068)</u>	<u>(7,663)</u>	<u>(2,536)</u>
<b>Financing activities</b>			
Issuance of preferred stock, net	—	23,763	—
Issuance of common stock, net	32,140	45	27
Payments under capital lease obligations	(788)	(413)	(323)
Payments on notes payable	—	(1,500)	—
Proceeds from capital lease obligations	1,179	864	757
Prepaid offering costs	—	(430)	—
Net cash flows provided by financing activities	<u>32,531</u>	<u>22,329</u>	<u>461</u>
Decrease in cash and cash equivalents	(96)	(1,063)	(7,744)
Cash and cash equivalents at beginning of year	11,017	12,080	19,824
Cash and cash equivalents at end of period	<u>\$ 10,921</u>	<u>\$ 11,017</u>	<u>\$ 12,080</u>
<b>Supplemental disclosure of cash flow information:</b>			
Interest paid	<u>\$ 214</u>	<u>\$ 232</u>	<u>\$ 211</u>
<b>Supplemental schedule of noncash investing and financing activities:</b>			
Shares tendered from stockholders for repayment of the principal and accrued interest of stockholder loans	<u>\$ —</u>	<u>\$ 514</u>	<u>\$ —</u>
Prepayment of convertible term loan principal and accrued interest with option fee offset	<u>\$ —</u>	<u>\$ —</u>	<u>\$ 2,035</u>
Preferred stock warrant issued in connection with equipment loan	<u>\$ —</u>	<u>\$ —</u>	<u>\$ 22</u>
Conversion of convertible preferred stock to common stock upon initial public offering	<u>\$ 64</u>	<u>\$ —</u>	<u>\$ —</u>
Deemed beneficial conversion feature for Series E preferred stock	<u>\$ —</u>	<u>\$ 24,900</u>	<u>\$ —</u>

*See accompanying notes.*

**METABASIS THERAPEUTICS, INC.**  
**NOTES TO FINANCIAL STATEMENTS**

**1. Organization and Summary of Significant Accounting Policies**

*Organization and Business*

Metabasis Therapeutics, Inc. ("Metabasis" or the "Company") is a biopharmaceutical company focused on the discovery, development and commercialization of novel small molecule drugs principally to treat metabolic diseases, cancer and certain other diseases linked to pathways in the liver.

*Use of Estimates*

The preparation of financial statements in conformity with accounting principles generally accepted in the United States requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities and disclosures of contingent assets and liabilities at the date of the financial statements. Estimates also affect the reported amounts of revenues and expenses during the reporting period. Actual results could differ from those estimates.

*Cash and Cash Equivalents*

Cash and cash equivalents consist of cash and highly liquid instruments with original maturities of three months or less when purchased.

*Securities Available-For-Sale*

Short-term investments are classified as available-for-sale and are carried at fair value, with unrealized gains and losses reported in stockholders' equity. The amortized cost of debt securities in this category is adjusted for amortization of premiums and accretion of discounts to maturity. Such amortization is included in interest income. Realized gains and losses and declines in value judged to be other-than-temporary, if any, on available-for-sale securities are included in other income. The cost of securities sold is based on the specific-identification method. Interest and dividends on securities classified as available-for-sale are included in interest income.

*Fair Value of Financial Instruments*

The carrying amount of cash and cash equivalents, securities available-for-sale, accounts receivable, accounts payable and accrued liabilities are considered to be representative of their respective fair values because of the short-term nature of those instruments. Based on the borrowing rates currently available to the Company for loans with similar terms, management believes the fair value of the long-term debt approximates its carrying value.

*Concentration of Credit Risks and Major Partners*

Financial instruments that potentially subject the Company to a significant concentration of credit risk consist primarily of cash and cash equivalents and securities available-for-sale. The Company invests its excess cash in U.S. government securities and debt instruments of financial institutions and corporations with strong credit ratings. The Company has established guidelines relative to diversification of its cash investments and their maturities that are intended to secure safety and liquidity. These guidelines are periodically reviewed and modified to take advantage of trends in yields and interest rates and changes in the Company's operations and financial position. To date, the Company has not experienced any impairment losses on its cash and cash equivalents or securities available-for-sale.

One collaborative partner individually accounted for 51%, 83%, and 91% of total revenues during the years ended December 31, 2004, 2003 and 2002 (see Note 5).

#### *Property and Equipment*

Property and equipment is carried at cost less accumulated depreciation. Depreciation is computed on the straight-line method and depending on asset classification, over a period of three to five years. Leasehold improvements are amortized over the estimated useful life of the asset or the lease term, whichever is shorter.

#### *Impairment of Long-Lived Assets*

The Company adopted Statement of Financial Accounting Standards ("SFAS") No. 144, *Accounting for the Impairment or Disposal of Long-Lived Assets*, as of the beginning of 2002. The adoption of this accounting standard did not have a material impact on the Company's operating results and financial position. The Company assesses potential impairments to its long-lived and intangible assets when there is evidence that events or changes in circumstances indicate that the carrying amount of an asset may not be recovered. There have been no indicators of impairment through December 31, 2004.

#### *Revenue Recognition*

The Company's revenue recognition policies are in accordance with the Securities and Exchange Commission Staff Accounting Bulletin ("SAB") 101, *Revenue Recognition in Financial Statements*, as amended by SAB 104, *Revenue Recognition*, and Emerging Issues Task Force ("EITF") Issue 00-21, *Revenue Arrangements with Multiple Deliverables*. Many of the Company's revenues are primarily related to collaborations with pharmaceutical companies. The Company's agreements generally contain multiple elements, including sponsored research funding, future milestone payments and royalties. All fees are nonrefundable.

Upfront, nonrefundable fees under the Company's collaborations and advance payments for sponsored research, which are in excess of amounts earned are classified as deferred revenue and are recognized as income over the period the related services are provided. Nonrefundable upfront fees, which do not require the Company's continuing involvement, or which do not contain future performance obligations, are recognized when received.

Amounts received for sponsored research funding are recognized as revenues as the services are performed. These agreements are on a best-efforts basis and do not require scientific achievement as a performance obligation and provide for payment to be made when costs are incurred or the services are performed.

Revenue from milestones is recognized when earned, provided that (i) the milestone event is substantive and its achievability was not reasonably assured at the inception of the agreement, and (ii) collaborator funding (if any) of the Company's performance obligations after the milestone achievement will continue at a level comparable to before the milestone achievement. If both of these criteria are not met, the milestone payment is recognized as revenue over the remaining minimum period of the Company's performance obligations under the agreement.

#### *Research and Development*

All costs of research and development, including those incurred in relation to the Company's collaborative agreements, are expensed in the period incurred. Research and development costs primarily consist of salaries and related expenses for personnel, outside service providers, fees paid to consultants and materials used in clinical trials and research and development.

### *Comprehensive Income or Loss*

SFAS No. 130, *Reporting Comprehensive Income*, requires that all components of comprehensive income or loss, including net income or loss, be reported in the financial statements in the period in which they are recognized. Comprehensive income or loss is defined as the change in equity during a period from transactions and other events and circumstances from nonowner sources. The Company's other comprehensive income (loss) for December 31, 2004, 2003, and 2002 consisted of unrealized gains and losses on available-for-sale securities and is reported in stockholders' equity.

### *Stock-Based Compensation*

The Company has elected to follow Accounting Principles Board Opinion No. 25 ("APB 25"), *Accounting for Stock Issued to Employees*, and related interpretations in accounting for its employee and director stock options. Under APB 25, if the exercise price of the Company's employee and director stock options equals or exceeds the estimated fair value of the underlying stock on the date of grant, no compensation expense is recognized. In conjunction with the Company's initial public offering completed on June 16, 2004, the Company reviewed its historical exercise prices through June 15, 2004 and, as a result, revised the estimate of fair value for the stock underlying all stock options granted subsequent to June 30, 2002. The weighted average exercise price for the 930,000 options granted to the Company's employees and directors during July 2002 through June 15, 2004 was \$1.46. With respect to employee and director options granted, the Company has deferred stock compensation balances of \$4.9 million and \$4.9 million at December 31, 2004 and 2003, respectively, for the difference between the original exercise price per share determined by the Board of Directors and the revised estimate of fair value per share at the respective grant dates. Deferred stock compensation is recognized and amortized on a straight-line basis over the vesting period of the related options, generally four years. Compensation expense related to stock options granted to the Company's employees and directors was approximately \$1.6 million, \$0.5 million, and \$23,000 for the twelve months ended December 31, 2004, 2003, and 2002, respectively.

Options or stock awards issued to nonemployees have been valued in accordance with SFAS No. 123, *Accounting for Stock-Based Compensation*, and Emerging Issues Task Force ("EITF") Issue 96-18, *Accounting for Equity Instruments that are Issued to Other than Employees for Acquiring, or in Conjunction with Selling Goods or Services*, and expensed over the period the services are provided. Deferred charges for options granted to non-employees are periodically remeasured as the options vest.

As required under SFAS No. 123, the pro forma effects of stock-based compensation on net income or loss were estimated at the date of grant using the minimum-value method for all grants made through June 15, 2004, the effective date of the Company's registration statement for its initial public offering, and the Black-Scholes method thereafter. The Company became a public company on June 16, 2004, and accordingly began using the Black-Scholes valuation model in accordance with SFAS No. 123. The minimum-value method and the Black-Scholes valuation model were developed for use in estimating the fair value of publicly traded options that have no vesting restrictions and are fully transferable. Because the Company's employee and director stock options have characteristics significantly different from those of publicly traded options, and because changes in the subjective input assumptions can materially affect the fair value estimate, in management's opinion, these existing models do not necessarily provide a reliable single measure of the fair value of the Company's employee and director stock options.

For purposes of pro forma disclosures, the estimated fair value of the options is amortized to expense over the vesting period of such stock options. The Company's pro forma information is as follows:

	Years Ended December 31,		
	2004	2003	2002
	(in thousands, except per share amounts)		
Net loss applicable to common stockholders as reported . . . . .	\$(14,972)	\$(34,329)	\$(12,797)
Add: Stock-based employee compensation expense included in reported net loss . . . . .	1,633	504	23
Deduct: Stock-based employee compensation expense determined under fair value method . . . . .	(1,802)	(537)	(39)
Pro forma net loss applicable to common stockholders . . . . .	<u>\$(15,141)</u>	<u>\$(34,362)</u>	<u>\$(12,813)</u>
Basic and diluted net loss per share as reported . . . . .	\$ (1.49)	\$ (23.84)	\$ (10.12)
Pro forma basic and diluted net loss per share . . . . .	\$ (1.51)	\$ (23.86)	\$ (10.13)

*Net Loss Per Share*

The Company calculated net income or loss per share in accordance with SFAS No. 128, *Earnings Per Share*. Basic earnings per share ("EPS") is calculated by dividing the net income or loss by the weighted average number of common shares outstanding for the period, without consideration for common stock equivalents. Diluted EPS is computed by dividing the net income or loss by the weighted average number of common share equivalents outstanding for the period determined using the treasury-stock method. For purposes of this calculation, common stock subject to repurchase by the Company, options, and warrants are considered to be common stock equivalents and are only included in the calculation of diluted earnings per share when their effect is dilutive.

The actual net loss per share amounts for the year ended December 31, 2004 were computed based on the shares of common stock outstanding during the year, including the 5.0 million shares of common stock issued in the Company's initial public offering on June 21, 2004, an additional 75,000 shares of common stock pursuant to the exercise by the underwriters of an over-allotment option on July 20, 2004 and the 11.0 million shares of the Company's common stock issued upon conversion of the Company's preferred stock in conjunction with the initial public offering. As a result of the issuance of these common shares, there is a lack of comparability in the basic and diluted net loss per share amounts for the periods presented below. In order to provide a more relevant measure of operating results, the following unaudited pro forma net loss per share calculation has been included. The shares used to compute unaudited pro forma basic and diluted net loss per share represent the weighted average common shares outstanding for the period, reduced by the weighted average unvested common shares subject to repurchase, and including the assumed conversion of all outstanding shares of preferred stock into shares of common stock using the as-if converted method as of the beginning of each year presented or the date of issuance, if later.

	Years Ended December 31,		
	2004	2003	2002
	(in thousands, except per share amounts)		
<b>Actual:</b>			
<i>Numerator:</i>			
Net loss .....	\$(14,972)	\$ (9,429)	\$(12,797)
Deemed dividend-beneficial conversion feature for Series E preferred stock .....	—	(24,900)	—
Net loss applicable to common stockholders .....	<u>\$(14,972)</u>	<u>\$(34,329)</u>	<u>\$(12,797)</u>
<i>Denominator:</i>			
Weighted average common shares .....	10,452	1,731	1,696
Weighted average unvested common shares subject to repurchase .....	(418)	(291)	(431)
Denominator for basic and diluted net loss per share .....	<u>10,034</u>	<u>1,440</u>	<u>1,265</u>
Basic and diluted net loss per share .....	<u>\$ (1.49)</u>	<u>\$ (23.84)</u>	<u>\$ (10.12)</u>
<b>Pro forma:</b>			
<i>Numerator:</i>			
Pro forma net loss .....	\$(14,972)	\$(34,329)	
<i>Denominator:</i>			
Shares used above .....	10,034	1,440	
Pro forma adjustments to reflect assumed weighted average effect of conversion of preferred stock .....	5,220	7,747	
Pro forma shares used to compute basic net loss per share ...	<u>15,254</u>	<u>9,187</u>	
Pro forma basic and diluted net loss per share .....	<u>\$ (0.98)</u>	<u>\$ (3.74)</u>	
<b>Historical outstanding antidilutive securities not included in diluted net loss per share calculation*:</b>			
Preferred stock .....	—	63,632	
Common stock subject to repurchase .....	459	437	
Options to purchase common stock .....	1,108	951	
Warrants .....	<u>8,016</u>	<u>8,016</u>	
	<u>9,583</u>	<u>73,036</u>	

\* Represents the historical amount of the securities and not the common stock equivalent number of shares.

#### *New Accounting Pronouncements*

In December 2004, the Financial Accounting Standards Board ("FASB") issued SFAS No. 123R, *Share Based Payment*. This statement is a revision to SFAS 123 and supersedes APB 25 and amends FASB Statement No. 95, *Statement of Cash Flows*. This statement requires a public entity to expense the cost of employee services received in exchange for an award of equity instruments. This statement also provides guidance on valuing and expensing these awards, as well as disclosure requirements of these equity arrangements. This statement is effective for the first interim reporting period that begins after June 15, 2005.

SFAS 123R permits public companies to choose between the following two adoption methods:

1. A “modified prospective” method in which compensation cost is recognized beginning with the effective date (a) based on the requirements of SFAS 123R for all share-based payments granted after the effective date and (b) based on the requirements of Statement 123 for all awards granted to employees prior to the effective date of SFAS 123R that remain unvested on the effective date, or
2. A “modified retrospective” method which includes the requirements of the modified prospective method described above, but also permits entities to restate based on the amounts previously recognized under SFAS 123 for purposes of pro forma disclosures either (a) all prior periods presented or (b) prior interim periods of the year of adoption.

As permitted by SFAS 123, the Company currently accounts for share-based payments to employees using APB 25's intrinsic value method and, as such, the Company generally recognizes no compensation cost for employee stock options. The impact of the adoption of SFAS 123R cannot be predicted at this time because it will depend on levels of share-based payments granted in the future. However, valuation of employee stock options under SFAS 123R is similar to SFAS 123, with minor exceptions. The impact on the results of operations and earnings per share had the Company adopted SFAS 123, is described in stock based compensation section of Note 1 above. Accordingly, the adoption of SFAS 123R's fair value method will have a significant impact on the Company's results of operations, although it will have no impact on the Company's overall financial position. SFAS 123R also requires the benefits of tax deductions in excess of recognized compensation cost to be reported as a financing cash flow, rather than as an operating cash flow as required under current literature. This requirement will reduce net operating cash flows and increase net financing cash flows in periods after adoption. Due to timing of the release of SFAS 123R, the Company has not yet completed the analysis of the ultimate impact that this new pronouncement will have on the results of operations, nor the method of adoption for this new standard.

In March 2004, the Emerging Issues Task Force reached a consensus on Issue No. 03-1, *The Meaning of Other-Than-Temporary Impairment and Its Application to Certain Investments*. EITF Issue No. 03-1 provides guidance on other-than-temporary impairment models for marketable debt and equity securities accounted for under SFAS No. 115, *Accounting for Certain Investments in Debt and Equity Securities*. The EITF developed a basic three-step model to evaluate whether an investment is other-than-temporarily impaired. The provisions of EITF Issue No. 03-1 were effective for the Company's third quarter of fiscal 2004 and subsequent fiscal periods and will be applied prospectively to all current and future investments. Quantitative and qualitative disclosures for investments accounted for under SFAS No. 115 are effective for the Company's fiscal year ending 2004 and subsequent fiscal periods. The adoption of EITF Issue No. 03-1 did not have a material effect on the Company's results of operations and financial condition.

In March 2004, the FASB issued EITF 03-1, *The Meaning of Other-Than-Temporary Impairment and Its Application to Certain Investments*. EITF 03-1, which was originally effective for interim and annual reporting periods beginning after June 15, 2004 requires a three-step model to determine other-than-temporary impairments for all current and future investments in marketable securities. In September 2004, the FASB delayed the requirement to record impairment losses under EITF 03-1 until new guidance is issued. The Company does not expect that the adoption of EITF 03-1 will have a material impact on its operating results and financial position.

## 2. Securities Available-For-Sale

Securities available-for-sale consists of the following (in thousands):

	December 31, 2004			Estimated Fair Value
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	
Corporate debt securities . . . . .	32,988	—	(54)	32,934
Total . . . . .	<u>\$32,988</u>	<u>\$—</u>	<u>\$(54)</u>	<u>\$32,934</u>

	December 31, 2003			Estimated Fair Value
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	
U.S government securities . . . . .	\$ 8,583	\$—	\$(1)	\$ 8,582
Corporate debt securities . . . . .	5,663	—	(5)	5,658
Total . . . . .	<u>\$14,246</u>	<u>\$—</u>	<u>\$(6)</u>	<u>\$14,240</u>

Gross realized gains and losses on available-for-sale securities were immaterial during the years ended December 31, 2004 and 2003.

	Amortized Cost	Estimated Fair Value
Due in one year or less . . . . .	\$28,338	\$28,296
Due after one year through five years . . . . .	4,650	4,638
	<u>\$32,988</u>	<u>\$32,934</u>

## 3. Property and Equipment

Property and equipment consisted of the following (in thousands):

	December 31,	
	2004	2003
Laboratory equipment . . . . .	\$6,420	\$5,357
Computers and electronics . . . . .	2,200	2,013
Office furniture and fixtures . . . . .	643	633
Leasehold improvements . . . . .	145	144
Construction in progress . . . . .	66	—
	9,474	8,147
Less: accumulated depreciation and amortization . . . . .	(7,120)	(6,420)
	<u>\$2,354</u>	<u>\$1,727</u>

Depreciation and amortization expenses, which include assets held under capital leases, were \$699,000, \$564,000, and \$424,000 for the years ended December 31, 2004, 2003 and 2002, respectively. Assets held under capital leases totaled approximately \$4.0 million and \$2.7 million at December 31, 2004 and 2003, respectively. The related accumulated amortization was approximately \$2.0 million and \$1.1 million at December 31, 2004 and 2003, respectively.

#### 4. Accrued Liabilities

Accrued liabilities consisted of the following (in thousands):

	December 31,	
	2004	2003
Accrued employee benefits . . . . .	\$1,077	\$ 905
Bonus accrual . . . . .	654	554
Accrued development expenses . . . . .	610	346
Accrued legal and patent fees . . . . .	286	431
Other accrued liabilities . . . . .	208	266
	<u>\$2,835</u>	<u>\$2,502</u>

#### 5. Collaborative Research and Development Agreements

##### *Sankyo*

In April 1997, the Company established a three-year research, development and commercialization agreement with Sankyo Company, Ltd., ("Sankyo") to develop novel FBPase inhibitors for the treatment of diabetes. In February 2000 and March 2001, the discovery research portion of the collaboration was extended to an additional year of funding at \$3.5 million before ending as scheduled in April 2002. The revenue was recognized in each year as the services were performed. Sankyo retained rights to select compounds discovered during the research discovery period and is responsible for funding any clinical development compound or compounds selected for development.

The Company will continue to receive certain payments upon the achievement of specified milestones under the development portion of the collaboration. As of December 31, 2004, the Company has achieved three developmental milestones triggering a total of \$6.5 million in payments from Sankyo. The first milestone was earned in 1998. The second milestone was earned in July 2001 and was entirely offset by a \$2.0 million pre-payment made by Sankyo in June 1999. The third milestone was earned in March 2004. If all clinical and regulatory milestones are achieved, and including \$20.25 million in license fees and sponsored research payments received to date under the agreement, and the \$7.25 million investment in Series A Preferred and the \$8.5 million option fee referred to below, the Company may be entitled to payments which total up to \$54.5 million.

Assuming a compound is successfully developed and commercialized, the Company would receive royalties on net sales. Sankyo will have exclusive, worldwide commercialization rights to those products selected for development and subsequently licensed. The Company would also have co-promotion rights in North America to any commercialized product, on terms to be negotiated.

In December 1997, Sankyo made an equity investment of \$7.25 million in exchange for 851,939 shares of the Company's Series A Convertible Preferred Stock ("Series A Preferred"). The shares can be exchanged for common shares of Sico Inc. ("Sico"), now an indirect wholly-owned subsidiary of Teva Pharmaceuticals Industries Ltd., ratably over a five-year period beginning in January 2001. The exchange rate would be calculated using a defined formula that is affected by the then current fair value of Sico shares. In February 2001, 2002, 2003, 2004 and finally in 2005, Sankyo exercised its right to exchange with Sico one fifth of its Series A Preferred (or in the case of 2005, Common Stock issued upon conversion of its Series A Preferred) in Metabasis for common shares of Sico.

In October 2002, the Company entered into the Option Agreement with Sankyo which granted Sankyo certain rights to back-up compounds and the first right to negotiate a new collaborative research, development and commercialization agreement for next generation compounds to treat diabetes. In exchange for granting Sankyo these rights, the Company received a nonrefundable

\$8.5 million option fee subject to a 25% credit against future milestone payments payable to the Company assuming a new collaborative agreement. At December 31, 2002, approximately \$5.5 million was recorded as deferred revenue of which approximately \$3.9 million was recorded as noncurrent deferred revenue. The Company amortized the option fee net of the \$2.1 million credit over the period of the Option Agreement.

The term of the option period commenced with the execution of the Option Agreement and ended 90 days after dosing the last patient in a 14-day Phase II clinical trial. In August 2003, Sankyo chose not to exercise its option to negotiate a new agreement for the discovery, development, and licensing of second generation gluconeogenesis inhibitors. As a result, the Company recognized all remaining deferred revenue associated with the option fee in August 2003 and the Company may now develop these compounds on its own or in collaboration with another company. The Company recognized approximately \$7.6 million and \$0.9 million of the option fee as license fee revenue for the years ended December 31, 2003 and 2002, respectively.

#### *Valeant*

In October 2001, the Company entered into a development and license agreement with Valeant Pharmaceuticals International ("Valeant") for the development and commercialization of pradefovir for the treatment of hepatitis type B. Under the agreement, Valeant was granted exclusive worldwide rights to develop and commercialize pradefovir. The agreement also included an initial nonrefundable license fee of \$2.0 million, \$1.0 million of which was paid on the closing date. The remaining \$1.0 million was paid in 2002. The Company recognized the \$2.0 million license fee in 2001 as there were no future performance obligations required under the agreement. Valeant is solely responsible for conducting and funding all development work. The Company will continue to receive certain payments upon Valeant's achievement of specified development, regulatory and commercial milestones and to receive royalties on any product sales that result from the collaboration. As of December 31, 2004, the Company has achieved developmental milestones triggering a total of \$2.0 million in payments from Valeant. The first milestone was earned in April 2003 and the second milestone was earned in April 2004. If all development, regulatory and commercial milestones are achieved, and including the \$2.0 million license fee, the Company may be entitled to payments which total up to \$20.0 million, plus royalties. In the third quarter of 2002, Valeant initiated human clinical trials of pradefovir. Pradefovir is currently being tested in patients with the disease.

#### *Merck*

In December 2003, the Company entered into a collaboration agreement with Merck & Co., Inc. ("Merck") to apply the Company's technology to certain Merck lead compounds with the goal of improving safety and efficacy of these compounds for the treatment of hepatitis type C. As part of the collaboration, Merck paid an initial non-refundable license fee of \$500,000 in January 2004, agreed to pay \$3.0 million within one year should Merck exercise a right to exclusivity and provided research support funding of approximately \$1.4 million during the first year of the research term. In January 2005, we entered into a letter agreement, which amended the agreement between us and Merck, at which time Merck choose not to exercise its right to exclusivity. The amended agreement provided the Company with, among other things, additional research support funding of approximately \$1.4 million through December 2005 (see Note 12-Subsequent Event). Merck will also pay milestones if specified development and regulatory events occur and pay royalties on product sales that result from this collaboration. If all milestones are achieved, and including the \$500,000 license fee, the approximately \$2.8 million in research support and an additional exclusive option, the Company may be entitled to payments which total up to approximately \$93.3 million, plus royalties. Merck is solely responsible for conducting and funding all development work for compounds resulting from this collaboration.

## 6. Commitments

The Company leases its office and research facilities and certain laboratory and electronic equipment under operating and capital lease agreements. The facility lease, under a sublease agreement with Sicor which expires in September 2005, provides for annual 3.5% rent increases over the term of the lease beginning in January 2002. The difference between the straight-line expense over the term of the lease and actual amounts paid are recorded as deferred rent. Included in other assets at December 31, 2004 and 2003 were deposits under this agreement of \$111,000 and \$99,000, respectively. Rent expense was approximately \$1.3 million for each of the years ended December 31, 2004, 2003 and 2002.

On December 21, 2004, the Company entered into a new lease agreement pursuant to which the Company will lease up to approximately 82,000 square feet of real estate space in San Diego, California consisting of laboratory and office space. The lease commences on the later of September 1, 2005, or the date that certain landlord-funded tenant improvements are satisfactorily completed, and has an initial term of 10 years unless extended or sooner terminated. The Company has options to extend the lease for two renewal periods of five years each. The Company's aggregate lease payments as contemplated by the lease through 2015, if there is no delay in the rent commencement date, will be approximately \$28.0 million.

In 2001, the Company entered into a \$650,000 equipment loan agreement with a financing company. This agreement was subsequently amended to increase the loan amount to approximately \$2.1 million. The proceeds were used to finance laboratory equipment, computer and electronic equipment, tenant improvements and furniture. The Company made drawdowns of approximately \$1.7 million before the amended equipment loan agreement ended on December 31, 2002. The equipment loan was collateralized by the related equipment acquired with the loan. Each drawdown had a payment term of 48 months with the interest rate being fixed at the funding date of each drawdown (9.58% to 12.05%).

In connection with the initial equipment loan and first amendment, warrants to purchase up to 53,938 shares of Series C Convertible Preferred Stock ("Series C Preferred") at \$1.25 per share were issued, of which 45,000 shares are exercisable at any time through June 16, 2007. The remaining warrant to purchase 8,938 shares of Series C Preferred is exercisable at any time through December 31, 2007. The cash exercise of these warrants will result in the issuance of 8,877 shares of the Company's common stock.

In conjunction with the second loan agreement amendment, the Company issued warrants to purchase 30,666 shares of Series D Convertible Preferred Stock ("Series D Preferred"). The warrants have an exercise price of \$1.50 per share and are exercisable at any time through June 16, 2007. The cash exercise of these warrants will result in the issuance of 5,290 shares of the Company's common stock.

The warrants issued by the Company in connection with the equipment loan and related amendments were accounted for under APB 14, *Accounting for Convertible Debt and Debt Issued with Stock Purchase Warrants* and EITF Issue 96-18, which requires the warrants to be recorded at their fair value. The fair value of the warrants was accounted for under SFAS 123 using the Black Scholes Valuation Model. The warrants were valued at \$59,000 using the following assumptions: risk-free interest rates of 4.59% to 4.97%, respectively; dividend yield of 0%; expected volatility of 70%; and a term of 1.7 to 5 years. The fair market value was recorded as a discount on the equipment loan and is being amortized to interest expense over the term of the equipment loan. The unamortized discount was \$9,000 and \$24,000 at December 31, 2004 and 2003, respectively.

In August 2003, the Company entered into a \$1.4 million equipment loan agreement with a financing company. This agreement was subsequently amended to increase the amount to \$3.4 million.

The proceeds are used to finance lab equipment, computer and electronic equipment and furniture. The loan is collateralized by the related equipment acquired with the loan. As of December 31, 2004, the Company had drawn down approximately \$2.0 million under the equipment loan agreement. Each drawdown had a payment term of 48 months with the interest rate being fixed at the funding date of each drawdown (8.62% to 10.40%).

Future minimum rental payments under capital and operating leases as of December 31, 2004, are as follows (in thousands):

	<u>Capital Leases</u>	<u>Operating Leases</u>
2005 .....	\$1,022	\$ 1,353
2006 .....	800	1,629
2007 .....	544	1,860
2008 .....	198	2,317
2009 .....	3	2,905
Thereafter .....	—	18,847
Total minimum lease payments, excluding discount .....	<u>2,567</u>	<u>\$28,911</u>
Less amount representing interest .....	<u>(332)</u>	
Present value of net minimum payments .....	2,235	
Less current portion, excluding discount of \$8 .....	<u>(842)</u>	
Long-term obligation under capital leases, excluding discount of \$1 .....	<u>\$1,393</u>	

## 7. Stockholders' Equity

### *Initial Public Offering*

On June 21, 2004, the Company completed an initial closing of its initial public offering in which it sold 5.0 million shares of common stock for proceeds of \$30.6 million, net of underwriting discounts and commissions and offering expenses. In addition, on July 20, 2004, the Company completed an additional closing of its initial public offering in which it sold an additional 75,000 shares of common stock pursuant to the exercise by the underwriters of an over-allotment option which resulted in proceeds of \$0.5 million, net of underwriting discounts and commissions.

### *Convertible Preferred Stock*

Effective immediately prior to the initial closing of the Company's initial public offering, shares of outstanding subordinated and Series A, C, D and E convertible preferred stock then outstanding were automatically converted into 11.0 million shares of common stock.

### *Authorized Capital Stock*

On June 21, 2004, the Company filed an amended and restated certificate of incorporation to provide for authorized capital stock of 100 million shares of common stock and 5 million shares of preferred stock.

### *Series E Preferred Stock Deemed Dividend*

The Series E Preferred financing, which closed in October 2003, involved the sale of preferred stock at a price per share below the anticipated initial public offering price contemplated in the filing. Accordingly, pursuant to EITF 98-5, *Accounting for Convertible Securities with Beneficial Conversion Features*, the Company recorded a deemed dividend on the Series E Preferred of \$24.9 million, which

was the difference between the gross proceeds from the Series E Preferred offering and the underlying value of the conversion shares (adjusted for a conversion price adjustment feature and limited to the proceeds allocated to the convertible instrument). The \$24.9 million deemed dividend was entirely recognized as an adjustment to net loss applicable to common stockholders since the preferred stock was convertible, at any time, at the option of the holder. In accordance with EITF 00-27, *Application of Issue No. 98-5 to Certain Convertible Instruments*, the Company calculated the deemed dividend of \$24.9 million using the most favorable conversion price of \$3.12 per conversion share.

#### *Warrants*

In conjunction with the Series C Preferred offering, the Company sold warrants to the Series C investors to purchase 4.5 million shares of Series C Preferred at a purchase price of \$0.01 per warrant resulting in proceeds of approximately \$45,000. The stock purchase warrants have an exercise price of \$1.00 per share and shall terminate December 31, 2007. The cash exercise of these warrants will result in the issuance of 735,670 shares of the Company's common stock

In conjunction with the Series D Preferred offering, the Company sold warrants to the Series D investors to purchase 3.5 million shares of Series D Preferred at a purchase price of \$0.01 per warrant resulting in proceeds of approximately \$35,000. The stock purchase warrants have an exercise price of \$1.50 per share and can be exercised until the earlier of October 18, 2008, or after the Company's common stock trades on a securities exchange or the Nasdaq National Market and the average closing price of such common stock over any consecutive 20-trading day period equals or exceeds \$27.34 (adjusted to reflect subsequent stock dividends, stock splits or recapitalizations). The cash exercise of these warrants will result in the issuance of 597,339 shares of the Company's common stock

Additional warrants were issued in connection with the issuance of the equipment loans (see Note 6).

None of the above issued warrants had been exercised through December 31, 2004.

#### *Equity Incentive Plan*

On June 21, 2004, the Company authorized 2,213,995 shares of its common stock for issuance upon exercise of options or restricted stock granted under the 2001 Equity Incentive Plan (the "Plan"). The Plan provides for the grant of stock options and restricted stock to officers, directors, and employees of, and consultants and advisors to, the Company. Options under the Plan may be designated as incentive stock options or nonstatutory stock options, generally vest over four years and expire ten years from the date of grant. In addition, incentive stock options may not be granted at prices less than 100% of the fair value on the date of grant. The number of vested options available for exercise as of December 31, 2004 and 2003 was 374,000 and 266,000, respectively.

#### *Directors' Stock Option Plan*

On June 21, 2004, the Company authorized 300,000 shares of its common stock for issuance upon exercise of options or restricted stock granted under the 2004 Non-Employee Directors' Stock Option Plan (the "Directors' Plan"). The Directors' Plan provides for the grant of stock options and restricted stock to directors of the Company. Options under the Directors' Plan are designated as nonstatutory stock options, generally vest from one to two years, and expire ten years from the date of grant. In addition, options granted under the Directors' Plan may not be granted at prices less than 100% of the fair value on the date of grant. The number of vested options available for exercise as of December 31, 2004 was 23,000.

The weighted-average remaining contractual life of the options outstanding under both plans at December 31, 2004 and 2003, was approximately 8.0 and 8.6, respectively. The estimated weighted

average fair value of stock options granted during 2004, 2003 and 2002 was \$6.32, \$9.84, and \$1.38, respectively.

At December 31, 2004 and 2003, respectively, a total of 1,026,000 and 232,000 shares of common stock remained available for issuance under both plans.

The following is a further breakdown of the options outstanding as of December 31, 2004 (in thousands, except per share data):

Ranges of Exercise Prices	Number of Options	Options Outstanding		Options Vested and Exercisable	
		Weighted Average Contractual Life	Weighted Average Exercise Price	Number of Options	Weighted Average Exercise Price
\$0.00 to \$0.90	40	4.9	\$0.30	40	\$0.30
\$0.91 to \$1.82	772	8.1	1.44	304	1.42
\$2.73 to \$3.64	30	3.4	3.04	30	3.04
\$5.46 to \$6.38	147	8.0	5.56	—	—
\$6.39 to \$7.29	118	9.5	6.62	23	6.50
Total	<u>1,107</u>	<u>8.0</u>	<u>\$2.54</u>	<u>397</u>	<u>\$1.72</u>

The following table summarizes stock option activity as follows (in thousands, except per share amounts):

	Shares	Weighted-average exercise price
Outstanding at December 31, 2001	299	\$1.01
Granted	240	\$1.46
Exercised	(26)	\$1.03
Canceled	(8)	\$0.98
Outstanding at December 31, 2002	505	\$1.22
Granted	540	\$1.46
Exercised	(66)	\$0.67
Canceled	(28)	\$1.50
Outstanding at December 31, 2003	951	\$1.39
Granted	445	\$4.19
Exercised	(255)	\$1.24
Canceled	(34)	\$1.45
Outstanding at December 31, 2004	<u>1,107</u>	<u>\$2.54</u>

As of December 31, 2004 and 2003, respectively, there were 56,000 and 0 shares of common stock outstanding pursuant to option exercises subject to repurchase by the Company.

### Employee Stock Purchase Plan

On June 21, 2004, the Company authorized 500,000 shares of its common stock for issuance under the 2004 Employee Stock Purchase Plan ("ESPP"). The ESPP provides for all eligible employees to purchase shares of common stock at 85% of the lower of the fair market value on the first day of each two year offering period or any purchase date during such offering period (generally held every six months during such period). Employees may authorize the Company to withhold up to 15% of their total compensation during each six-month purchase period, subject to certain limitations. As of December 31, 2004, 30,000 shares were issued under the plan at a purchase price of \$5.95 per share, and 470,000 shares were reserved for future issuance.

### Shares Reserved For Future Issuance

The following shares of common stock were reserved for future issuance at December 31, 2004 (in thousands):

Warrants to purchase Series C Preferred .....	745
Warrants to purchase Series D Preferred .....	603
Common stock options:	
Granted and outstanding .....	1,107
Reserved for future issuance .....	1,026
Employee stock purchase plan .....	470
	<u>3,951</u>

## 8. Income Taxes

Significant components of the Company's deferred tax assets as of December 31, 2004 and 2003 are shown below (in thousands). A valuation allowance of \$22.9 million and \$16.5 million has been established at December 31, 2004 and 2003, respectively, to offset the net deferred tax assets as realization is uncertain.

	December 31,	
	2004	2003
Deferred tax assets:		
Net operating loss carryforwards .....	\$19,087	\$13,564
Research and development credits .....	3,523	2,603
Deferred revenue .....	—	187
Other, net .....	422	403
Total deferred tax assets .....	<u>23,032</u>	<u>16,757</u>
Deferred tax liabilities:		
Deferred compensation .....	(174)	(269)
Total deferred tax liabilities .....	<u>(174)</u>	<u>(269)</u>
Valuation allowance for deferred tax assets .....	<u>(22,858)</u>	<u>(16,488)</u>
Net deferred assets .....	\$ —	\$ —

At December 31, 2004, the Company had federal and California net operating loss carryforwards of \$46.8 million and \$47.1 million, respectively, which will begin to expire in 2020 and 2008, respectively, unless previously utilized. The Company also had federal and state research and development tax credit carryforwards of approximately \$2.2 million and \$1.9 million respectively. The

federal research and development tax credit carryforwards will begin expiring in 2020 unless previously utilized and the state credits do not expire.

Pursuant to Section 382 of the Internal Revenue Code, use of the Company's net operating loss and credit carryforwards may be limited since cumulative changes in ownership of more than 50% have occurred within a three-year period. However, the Company does not believe such limitations will have a material impact on the utilization of these carryforwards.

## **9. Related Party**

In June 1999, the Company entered into an agreement with Sicor called the Master Agreement under which, among other things, the Company agreed to pay Sicor a 2% royalty on sales of products that would infringe on one of the Company's patents, patent applications, discoveries or inventions in existence as of the Company's restructuring, and 10% on any royalties the Company receives from licenses of these patents, patent applications, discoveries or inventions. The Company also agreed to pay Sicor a 1% royalty on sales of products that use, contain or are based on the Company's trade secrets, know-how and other proprietary rights in existence as of the Company's restructuring that are not covered by the 2% royalty, and 5% of any royalties the Company receives from licenses of these trade secrets, know-how and other proprietary rights that are not covered by the 10% royalty. Some or all of the Company's current product candidates and drug compounds from our research programs may be subject to these royalty provisions.

In June 1999, the Company extended approximately \$425,000 in full recourse promissory notes (the "Notes") to the Founders related to the purchase of an aggregate of 1,646,248 shares of the Company's common stock (the "Shares"). The Notes accrued interest at a rate of 5.22% per annum. The entire principal balance of the Notes, together with all accrued and unpaid interest, was due on June 30, 2003. The Shares, which are held by the Company as security for the Founders' obligations under the Notes, were subject to monthly vesting over four years (with a one-year "cliff"), expiring in June 2003. The vesting of the Shares was subject to acceleration upon a change of control followed by either an involuntary termination without cause or a voluntary termination for good reason.

In 2003, the Board of Directors authorized a transaction, effective June 30, 2003, calling for the Founders to agree to tender 487,702 shares of their previously vested common stock and subject them to a new monthly vesting schedule over a four-year period commencing on June 30, 2003. This transaction was entered into as repayment for outstanding principal and accrued interest on the Notes of approximately \$514,000 and related taxes paid on their behalf by the Company. The amount of shares tendered was based upon the then fair value for the common stock as determined by the Board of Directors. The Company recorded approximately \$711,000 of deferred compensation at June 30, 2003, to be amortized over the four-year vesting period of the underlying common stock. The Company has deferred compensation balances associated with this transaction of approximately \$444,000 and \$622,000 at December 31, 2004 and 2003, respectively. The Company recorded amortization of deferred compensation of approximately \$178,000, \$89,000 and \$0 for the years ended December 31, 2004, 2003 and 2002, respectively. The amortization of deferred compensation will be approximately \$178,000, \$178,000 and \$88,000 for the periods ended December 31, 2005, 2006 and 2007, respectively. As of December 31, 2004, the unvested balance of shares subject to repurchase by the Company was 46,853, 124,022 and 133,944 held by Mr. Beck and Drs. Erion and Laikind, respectively.

In 2000, 2001 and 2002, the Company made advances of \$50,000, one each year, to three employees of the Company. Each advance has a term of four years and bears an annual interest rate of 5.87%, 4.94% and 3.46% for 2000, 2001 and 2002, respectively. As of December 31, 2004, one of the advances had been repaid to the Company and two of the advances were outstanding.

## 10. Employee Benefit Plan

The Company established a defined contribution employee retirement plan (the "401(k) Plan") effective January 1, 1999, conforming to Section 401(k) of the Internal Revenue Code ("IRC"). All full-time employees (as defined in the 401(k) Plan) may elect to have a portion of their salary deducted and contributed to the 401(k) Plan up to the maximum allowable limitations of the IRC, which may be matched by the Company in an amount determined by the Board of Directors. No such Company matching contributions have been approved or made since the inception of the 401(k) Plan.

## 11. Summary of Quarterly Financial Data (Unaudited)

The following is a summary of the quarterly results of operations for the years ended December 31, 2004 and 2003 (in thousands, except for net (loss) income per share data):

	Quarters Ended				Year Ended Dec 31
	First Quarter	Second Quarter	Third Quarter	Fourth Quarter	
<b>2004</b>					
Revenue .....	\$4,170	\$1,771	\$ 470	\$ 426	\$ 6,837
Total operating expenses .....	4,691	5,414	5,638	6,369	22,112
Net loss attributable to common stockholders .....	(512)	(3,633)	(5,052)	(5,775)	(14,972)
Basic and diluted net loss per share: .....	(0.37)	(1.17)	(0.29)	(0.32)	(1.49)
<b>2003</b>					
Revenue .....	\$ 944	\$2,022	\$ 5,837	\$ 321	\$ 9,124
Total operating expenses .....	4,316	4,343	4,696	5,152	18,507
Net (loss) income attributable to common stockholders .....	(3,364)	(2,327)	1,114	(29,752)	(34,329)
Net (loss) income per share: (1)					
Basic .....	(2.19)	(1.42)	0.88	(22.47)	(23.84)
Diluted .....	(2.19)	(1.42)	0.76	(22.47)	(23.84)

(1) The sum of the four quarters may not necessarily agree to the year total due to rounding within a quarter.

## 12. Subsequent Event (Unaudited)

### *Merck*

On January 21, 2005, the Company entered into a letter agreement (the "Amendment") amending the Exclusive License and Research Collaboration Agreement dated December 23, 2003 (the "Collaboration Agreement") between the Company and Merck. Under the Collaboration Agreement, the Company is creating prodrugs of certain compounds that Merck is supplying that target the hepatitis C virus residing in the liver.

Among other things, the Amendment (i) extends the research term under the Collaboration Agreement for an additional one-year period through December 2005, (ii) increases the number of compounds that Merck will supply to the Company under the Collaboration Agreement during the extended research term and (iii) expands the scope of the technology that the Company will apply to compounds supplied to us by Merck under the Collaboration Agreement during the extended research term.

We are a biopharmaceutical company focused on the discovery, development and commercialization of novel small molecule drugs principally to treat metabolic diseases, cancer and certain other diseases linked to pathways in the liver. Examples of common metabolic diseases we are targeting include diabetes, hyperlipidemia and obesity - liver diseases include primary liver cancer, hepatitis B, hepatitis C, and fibrosis.

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