MEDICINES CO/ MA
Form 10-K405
April 01, 2002

SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, D.C. 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)

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

For the fiscal year ended: December 31, 2001

OR

| | 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 000-31191

THE MEDICINES COMPANY
(Exact name of registrant as specified in its charter)

DELAWARE	04-3324394
(State or other jurisdiction of incorporation or organization)	(I.R.S. Employer Identification No.)
5 SYLVAN WAY, SUITE 200 PARSIPPANY, NEW JERSEY	07054
(Address of principal executive offices)	(Zip Code)

Registrant's telephone number, including area code: (973) 656-1616

Securities registered pursuant to Section 12(b) of the Act: NONE

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

COMMON STOCK, $.001 PAR VALUE
(Title of each class)

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 |X| 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 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. |X|

The aggregate market value of voting Common Stock held by non-affiliates

of the registrant was $224,188,562 based on the last reported sale price of the Common Stock on the Nasdaq National Market on March 27, 2002.

Number of shares of the registrant's class of Common Stock outstanding as of March 27, 2002: 34,757,701.

DOCUMENTS INCORPORATED BY REFERENCE:

Document Description	10-K Part
Portions of the Registrant's Proxy Statement for the 2002 Annual Meeting of Stockholders	Part III

THE MEDICINES COMPANY
ANNUAL REPORT ON FORM 10-K
FOR THE FISCAL YEAR ENDED DECEMBER 31, 2001

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PART I

ITEM 1. BUSINESS

OVERVIEW

We operate as a pharmaceutical company selling and developing products for the treatment of hospital patients. We acquire, develop and commercialize biopharmaceutical products that are in late stages of development or have been

approved for marketing. We began selling Angiomax, our lead product, in U.S. hospitals in January 2001 as an anticoagulant replacement for heparin, selling $14.2 million of Angiomax in 2001. In December 2000, we received marketing approval from the United States Food and Drug Administration, or FDA, for Angiomax for use as an anticoagulant in combination with aspirin in patients with unstable angina undergoing coronary balloon angioplasty. Coronary balloon angioplasty is a procedure that is used to restore normal blood flow in an obstructed artery in the heart.

Our hospital sales force of 85 people targets approximately 750 hospitals in the United States that perform 200 or more coronary angioplasties per year. We are seeking to broaden Angiomax sales using educational programs, preceptorships in leading medical centers, publications, clinical trials and support for investigator-initiated studies. We plan to leverage our sales presence in these hospitals by expanding the uses of Angiomax beyond the cardiac catheterization laboratory into the operating room and for the emergency treatment of ischemic heart disease patients, and by seeking to acquire and develop additional pharmaceutical products that our hospital sales force can sell. In 2002, we acquired rights from AstraZeneca AB to clevidipine, an intravenous compound for the short term control of high blood pressure, for which Phase 3 clinical trials are planned.

We are developing Angiomax for additional potential hospital applications as a procedural anticoagulant and for use in the treatment of ischemic heart disease, a condition which occurs when organs receive an inadequate supply of oxygen as a result of decreased blood flow. As of March 15, 2002, clinical investigators had administered Angiomax to approximately 14,000 patients in clinical trials in the treatment and prevention of blood clots in a wide range of hospital applications. We believe that Angiomax can become the leading replacement for heparin in hospital care. In the United States, heparin is the most widely-used acute care anticoagulant and is used to treat over seven million hospitalized patients per year.

Angiomax directly blocks or inhibits the actions of thrombin, a key component in the formation and growth of blood clots. Thrombin is a factor central to the clotting process because it plays an essential role in the formation of fibrin, a protein that forms the mesh of a blood clot, and because thrombin is a potent activator of platelets which clump around fibrin as a blood clot forms. By blocking thrombin directly, rather than indirectly like heparin, Angiomax inhibits the actions of thrombin both in the clot and in the blood. The inhibition of thrombin by Angiomax is reversible, which means that its thrombin-blocking effect wears off over time, allowing thrombin to again work in the clotting process. This reversibility is associated with a reduced risk of bleeding.

In clinical trials in angioplasty, Angiomax has:

- reduced the frequency of life-threatening coronary events including heart attack and the need for emergency coronary procedures;
- reduced the likelihood of major bleeding and the need for blood transfusion;
- demonstrated a predictable anticoagulant response to a specific Angiomax dose, which enables simplified dosing; and
- been used in combination with GP IIb/IIIa inhibitors and other products used in angioplasty, demonstrating no evidence of significant interactions.

Our strategy is to build a commercial biopharmaceutical operation by acquiring, developing and commercializing development-stage or approved products that make

a clinical difference to hospitalized patients. In acquiring development-stage products, we seek to acquire late-stage products with

(1) existing clinical data which provides reasonable evidence of safety and efficacy, (2) an anticipated time to market of four years or less and (3) potential cost savings to payors or improved efficiency of patient care.

ANGIOMAX

Overview

In December 2000, we received marketing approval from the FDA for Angiomax for use as an anticoagulant in combination with aspirin in patients with unstable angina undergoing coronary balloon angioplasty. We began selling Angiomax in the United States in January 2001. In September 1999, Angiomax was approved in New Zealand for use in the treatment of patients undergoing coronary balloon angioplasty.

We believe Angiomax will be a valuable replacement to heparin, an anticoagulant used in almost all angioplasty procedures performed in the United States, used in most major cardiac and vascular surgical procedures in the United States and administered to a majority of patients treated in hospitals in the United States for acute coronary syndromes, including heart attack. As of March 15, 2002, clinical investigators had administered Angiomax to approximately 14,000 patients in clinical trials for the treatment and prevention of blood clots in a wide range of hospital applications. In clinical trials in angioplasty, use of Angiomax compared to heparin has resulted in fewer life-threatening coronary events and fewer bleeding events, including a reduction in the need for blood transfusion. The therapeutic effect of Angiomax is more predictable than heparin, which enables simplified dosing. The therapeutic benefit of Angiomax is strongest in high-risk patients who have previously experienced a heart attack or unstable angina.

We believe that Angiomax has additional potential applications for the treatment of ischemic heart disease and for use as a procedural anticoagulant. At present, we:

- are conducting a randomized double blind Phase 3b/4 trial program in angioplasty comparing Angiomax with the provisional use of a GP IIb/IIIa inhibitor, at the choice of the physician, to heparin plus a GP IIb/IIIa inhibitor;

- are conducting a Phase 3 trial program studying the use of Angiomax in the treatment of patients undergoing angioplasty who experience reduced platelet count and clotting due to an immunological reaction to heparin, known as heparin-induced thrombocytopenia and heparin-induced thrombocytopenia and thrombosis syndrome, or HIT/HITTS;

- are conducting a Phase 2 trial program studying the use of Angiomax as an anticoagulant in patients undergoing coronary artery bypass graft surgery, or CABG, without the use of a bypass pump;

- plan to commence a Phase 3 trial program to study the use of Angiomax in HIT/HITTS patients undergoing CABG, with and without the use of a bypass pump;

- plan to commence a randomized Phase 3 trial program to study the use of Angiomax in emergency patients for whom angioplasty is planned and who are at high risk due to a heart attack or unstable angina; and

- plan to commence a Phase 2 trial program in prematurely born babies with active thrombosis.

Through the Angiomax Foundation Program we are also supporting investigator-initiated studies of Angiomax in angioplasty patient groups where the clinical and economic limitations of heparin are likely to be most significant.

Background

Clotting. Normally, blood loss at the site of an injury is limited by the formation of blood clots, or thrombosis. In general, clotting serves a life-saving function by reducing bleeding, but sometimes unwanted clots in arteries can lead to heart attack, stroke or organ failure. A blood clot is a collection of cross-linked strands of a protein called

fibrin that forms a mesh around activated platelets and red blood cells. Blood clots are formed through precisely regulated interactions among the blood vessel wall, plasma clotting factors, including thrombin and fibrinogen, and platelets.

The trigger for the clotting process in an artery is typically a tearing or spontaneous rupture which exposes cholesterol and fat deposited on a blood vessel wall to the bloodstream. This may happen without an apparent cause or may be caused as a direct result of, for example, an angioplasty procedure. In parallel, the clotting factor, thrombin, is activated, and a thin protective layer of platelets is deposited at the rupture site. Thrombin activates platelets, thrombin and platelets interact, and thrombin formation, fibrin formation and platelet clumping take place. A full-blown clot may form rapidly. As a clot blocks the blood vessel it may then cut off blood supply to the heart muscle, to the brain or to other organs. If a clot blocks blood supply to the heart muscle, the muscle stops working either in part, which is a heart attack, or myocardial infarction, or completely, which may lead to cardiac arrest as the heart stops beating. This may result in irreversible damage to the heart or death.

During medical procedures such as coronary angioplasty, the blood clotting process must be slowed to avoid unwanted clotting in the coronary artery, and the potential growth or movement of a clot along blood vessels to new sites.

The trigger for clotting in veins is usually slower than that in arteries. In general, venous clots are caused by slow blood flow, which typically occurs when patients are immobilized, such as after surgery and during pregnancy, or when patients experience changes in the blood as a result of diseases such as cancer. When a clot develops in large, deep veins, which return blood to the heart by way of the lungs, this condition is referred to as deep vein thrombosis. In some cases of deep vein thrombosis, part of the clot may break off and move to the lungs with potentially fatal results.

Anticoagulation Therapy. Anticoagulation therapy attempts to modify actions of the components in the blood system that cause clot-forming factors leading to blood clots. The most important approach to the prevention and management of arterial and venous clots is diet and exercise. When the risks of clot formation cannot be avoided, or when medical procedures such as angioplasty almost guarantee some degree of increased risk of clots, anticoagulation therapy is indicated. Anticoagulation therapy involves the use of drugs to inhibit one or more components of the clotting process, thereby reducing the risk of clot formation. Anticoagulation therapy is usually started immediately after a diagnosis of blood clots or after risk factors for clotting are identified. Because anticoagulation therapy reduces clotting, it also may cause excessive

bleeding.

To date, three principal components of the clotting process, thrombin, fibrin and platelets, have been targeted for anticoagulation therapy:

- The actions of thrombin in the clotting process may be inhibited by indirect thrombin inhibitors, such as heparin, which act to turn off coagulation factors and turn on natural anti-clotting factors such as antithrombin-III, or AT-III. The actions of thrombin in the clotting process also may be inhibited by direct thrombin inhibitors, which act directly on thrombin. Because thrombin activates platelets, direct thrombin inhibitors also prevent platelet clumping.

- Fibrin may be dissolved after clotting has occurred by products called fibrinolytics.

- The aggregation of platelets in the clotting process may be inhibited by products called platelet inhibitors, which act on different pathways, including specific enzyme pathways like the cyclo-oxygenase and the adenosine diphosphate, or ADP, pathways and surface sites like the GP IIb/IIIa receptor.

Drugs are currently used alone or in combination with other anticoagulant therapy to target one or more components of the clotting process. These drugs have anticoagulant effects but also increase the patient's risk of bleeding due to the high doses needed to produce anticoagulant effects. In order to reduce this risk, physicians increasingly use combinations of drugs targeted at different components of the clotting process at lower doses, which reduce the risk of thrombosis while minimizing the risk of bleeding.

Indirect Thrombin Inhibitors. In the hospital environment, most patients undergoing anticoagulation therapy for the prevention and treatment of arterial and venous thrombosis receive heparin or low molecular weight heparin. In the United States, over seven million hospitalized patients annually receive heparin. Heparin is a standard component of acute anticoagulation therapy because of the central role of thrombin in the clotting process and heparin's rapid anticoagulant effect.

Heparin's properties as an anticoagulant were discovered in 1916. It is prepared from the intestines of pigs or cows. Heparin is a complex mixture of animal-derived sugars with variable anticoagulant potencies. The anticoagulant effects of heparin on any given patient are difficult to predict because heparin binds non-specifically to human cells and circulating substances in the blood. For these and other reasons, heparin, as a non-specific, indirect thrombin inhibitor, presents a variety of clinical challenges including:

- Weak effect in clots. Because it is an indirect thrombin inhibitor, heparin is ineffective on thrombin when clots have formed.

- Activates platelets. Heparin has been shown to enhance the clumping of platelets in unstable angina patients.

- Risk of bleeding. Patients who receive heparin have a high incidence of bleeding. This is particularly the case with patients who are elderly, female or have low body weight. Recent clinical trials have shown that bleeding risk may also be increased when heparin is used in combination with intravenous platelet inhibitors.

- Unpredictability. The anticoagulant effect of a given dose of heparin is unpredictable and therefore requires close monitoring.

- Adverse reaction risk. Heparin can cause HIT/HITTS, a dangerous immunological reaction.

- Diminished effect in sick patients. Heparin's effect may be reduced in the presence of blood factors found in patients stressed by disease, such as heart attack patients.

- Requires other factors for effect. Heparin can only bind to thrombin by first binding to a blood factor called antithrombin-III, which may be absent or present in insufficient amounts in some patients. Antithrombin-III deficiency is often severe or unpredictable in infants and children.

- Limitations in patients with impaired kidney function. Heparin is dependent on the kidney for clearance from the body. Among patients with impaired kidney function, unpredictability in the dosing of heparin leads to an excess in bleeding and thrombotic risk. Because kidney disease is associated with ischemic heart disease, these limitations of heparin are clinically important in patients undergoing angioplasty.

Physicians are increasingly using low molecular weight heparins as an alternative to heparin, especially as chronic therapy. In contrast to heparin, low molecular weight heparins tend to be more specific in their effect and may be administered once or twice daily by subcutaneous injection on an outpatient basis. Despite these advantages, low molecular weight heparins exhibit similar clinical challenges to those of heparin, including a weak effect in a clot that has already formed and a comparable risk of bleeding. In addition, clinicians are currently unable to monitor the anticoagulant effects of low molecular weight heparins, making their use in angioplasty problematic.

Angiomax Potential Advantages

Angiomax is a synthetic peptide of 20 amino acids that is a quick-acting, direct and specific inhibitor of thrombin and is administered by intravenous injection. Angiomax is specific in that it only binds to thrombin and does not bind to any other blood factors or cells.

Angiomax was engineered based on the biochemical structure of hirudin, a natural 65-amino acid protein anticoagulant. However, Angiomax is reversible while hirudin is not. This reversibility is associated with a reduced risk of bleeding.

Angiomax has numerous clinical advantages over heparin including:

- Effective in clots. Angiomax, as a direct thrombin inhibitor, is equally effective on thrombin in the clot as well as thrombin circulating in the blood;

- Inhibits platelets. Angiomax directly inhibits thrombin which is a potent activator of platelets;

- Reduced bleeding risk. As a reversible thrombin inhibitor, Angiomax has consistently shown clinically meaningful reductions in bleeding as compared to heparin;

- Predictability. A specified dose of Angiomax results in a predictable level of anticoagulation;

- Diminished adverse reaction risk. To date, Angiomax has not caused dangerous immunological reactions in clinical trials;

- Effective in sick patients. Angiomax is effective even in the presence of blood factors found in patients stressed by disease, such as heart attack patients;

- Independent of other factors for effect. Unlike heparin, Angiomax's effect does not require the presence of AT-III or any other factors to act on thrombin; and

- Predictable and effective in patients with impaired kidney function. As a direct and reversible thrombin inhibitor, Angiomax can be administered reliably in patients with impaired kidney function, resulting in reduced thrombotic and bleeding complications as compared to heparin.

Angiomax Potential Applications

We believe that Angiomax will become the leading replacement for heparin in acute cardiovascular care. We are commercializing Angiomax first for use in patients undergoing coronary angioplasty. In addition, we are developing Angiomax for use as an alternative to heparin as a procedural anticoagulant and for the hospital treatment of acute coronary syndromes. At present we have a Phase 3b/4 trial called REPLACE-2 underway in angioplasty, a Phase 3 angioplasty trial underway in HIT/HITTS, a Phase 2 trial underway in CABG without the use of a bypass pump and plans to study the use of Angiomax in high risk emergency patients for whom angioplasty is planned, in HIT/HITTS patients undergoing CABG and in prematurely born babies with active thrombosis. Our development plan is designed to highlight the clinical benefits of Angiomax initially in broad patient populations who are being treated with heparin and are at high risk of clots, bleeding or immunological reactions. We are also investigating other applications of Angiomax as an acute care product.

Use of Angiomax in Angioplasty

Angioplasty. Angioplasty is a procedure involving the inflation of a balloon or deployment of a stent or other device inside an obstructed artery to restore normal blood flow. The coronary angioplasty procedure itself increases the risk of coronary clotting, potentially leading to myocardial infarction, or MI, CABG, or death.

Based on hospital reimbursement data, in the United States in 2000 there were approximately 1,867,000 patients undergoing a procedure in a cardiac catheterization laboratory, including 813,000 coronary angioplasty patients. We believe that approximately forty-two to fifty percent of patients undergoing angioplasty were admitted through the emergency room and may be categorized as high risk. Many of these high-risk patients have previously experienced a heart attack or have unstable angina.

To prevent clotting, anticoagulation therapy is routinely administered to patients undergoing angioplasty. Heparin is currently used as an anticoagulant in virtually all patients undergoing angioplasty. In addition, platelet inhibitors such as aspirin, an ADP inhibitor or a GP IIb/IIIa inhibitor are often administered.

A segment of patients undergoing angioplasty and receiving anticoagulation therapy are at risk of significant bleeding. For example, bleeding risk is greater for patients who are elderly, female or underweight. Many patients undergoing angioplasty have impaired kidney function, making the use of heparin problematic.

Angiomax Clinical Experience in Angioplasty. We and the licensor of Angiomax, Biogen, have conducted or are conducting clinical trials of Angiomax in over 7,700 patients undergoing angioplasty. These trials have shown that Angiomax is a predictable anticoagulant, which can be used in combination with other therapies and which results in fewer adverse clinical events when compared to heparin.

A total of 6,134 patients have been treated in Angiomax trials completed in angioplasty. These trials have included patients treated with a variety of platelet inhibitors and patients in whom stents have been deployed. When measured seven days after treatment in the hospital, in comparison to heparin-treated patients in the trials, Angiomax-treated patients experienced:

- 43% fewer clinical events as measured by death, MI, revascularization procedures or major bleeding;
- 24% fewer ischemic events as measured by death, revascularization or MI; and
- 63% less bleeding.

The following table summarizes the combined clinical results for these patients.

	ANGIOMAX	HEPARIN	P-V
Number of patients	3,277	2,857	
In hospital up to 7 days			
Death, MI, revascularization or major bleeding	7.4%	13.0%	(less th
Death, MI or revascularization	5.7%	7.5%	0.
Death or MI	3.4%	4.4%	0.
Revascularization	3.3%	4.8%	0.
Major bleeding	2.8%	7.6%	(less th

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* The statistical significance of clinical results is determined by a widely-used statistical method that establishes the p-value of clinical results. For example, a p-value of less than 0.01 (p(less than)0.01) means that the chance of the clinical results occurring by accident is less than 1 in 100.

CACHET-B/C Trials in Angioplasty. In February 2000, we completed the CACHET-B/C study, a 210 patient randomized, multicenter study, in angioplasty. The trial analyzed the use of Angiomax versus low-dose heparin. All heparin patients also received ReoPro, a GP IIb/IIIa inhibitor. Although Angiomax patients could receive ReoPro under certain circumstances, physicians in the trial opted not to use ReoPro in 76% of the Angiomax patients.

The CACHET-B/C patient study population was broader than in earlier Angiomax trials, targeting lower risk patients undergoing angioplasty with expected stenting. Heparin and Angiomax doses were designed to achieve similar levels of anticoagulation. Aspirin with Ticlid or Plavix were used as platelet inhibitors in most patients. As in previous trials, Angiomax provided predictable levels of

dose response anticoagulation.

The combined incidence of death, MI, revascularization or major bleeding reported within seven days was 3.5% in Angiomax patients and 14.3% in heparin and ReoPro patients with a p-value of 0.013.

Low platelet count, or thrombocytopenia, was significantly less frequent among Angiomax patients than among heparin/ReoPro patients with a p-value of 0.012. Other adverse events occurred with similar frequency in both groups. Angiomax showed no apparent pharmacological interaction with ReoPro.

The results of the CACHET-B/C study provide support for the use of Angiomax as a foundation anticoagulant for angioplasty. In this study, Angiomax demonstrated predictable reversible anticoagulation and improved net clinical benefit over heparin. In addition, by decreasing major bleeds and reducing the need for revascularization and drug costs, we believe that, on average, substantial cost savings are possible for hospitals treating patients with Angiomax.

REPLACE-2 Trial in Angioplasty. In November 2001, we commenced the REPLACE-2 trial, which is a randomized double blind study in at least 6,000 patients who have been referred for angioplasty in 200 to 300 sites in the United States and eight other countries. REPLACE-2 includes two randomized arms:

- heparin with a GP IIb/IIIa inhibitor; and
- Angiomax with the provisional use of a GP IIb/IIIa inhibitor at the choice of the physician.

We plan to complete the REPLACE-2 trial in 2002.

Angiomax Commercial Operations in Angioplasty. We are selling Angiomax in the United States with a hospital sales force of 85 people. We began selling Angiomax in the United States in January 2001 using a sales force of 52 people contracted from Innovex, Inc., which we managed. In October 2001 we terminated our agreement with Innovex, hired members of the Innovex sales force as our employees and increased the size of our sales force.

We are focusing our Angiomax marketing efforts on interventional cardiologists and other key clinical decision-makers. Our sales force has been configured to target the approximately 750 hospitals with cardiac catheterization laboratories in which most of the angioplasty procedures in the United States are performed.

We expect Angiomax to provide cost savings to medical decision-makers who use Angiomax as part of a safe and effective anticoagulant therapy. Many United States hospitals receive a fixed reimbursement amount for the angioplasties they perform. Because this amount is not based on the actual expenses the hospital incurs, the use of Angiomax has the potential to reduce a hospital's cost of treating an angioplasty patient by reducing bleeding and ischemic events and reducing the need for other treatment therapies. From 1995 to 1997, the incremental costs to a hospital averaged the following: approximately $12,000 for an angioplasty patient receiving a 2-unit transfusion; approximately $4,000 for revascularization in the form of a repeat angioplasty; and approximately $17,000 for an angioplasty patient revascularized by means of coronary artery bypass graft surgery. Our pricing structure for Angiomax is designed to provide hospitals with cost savings based on reductions in clinical events, reductions in the use of other drugs, reductions in length of hospital stay, reduced need for lab tests and earlier patient ambulation.

If Angiomax is approved for use in other indications, we intend to market

Angiomax for these indications in the United States by supplementing our commercial organization, or by collaborating with other biopharmaceutical companies.

We plan to market, sell and distribute Angiomax outside of the United States through commercial partners. At present we have distribution agreements for Angiomax covering 59 countries. We have entered into an exclusive collaboration with Nycomed Danmark A/S for the distribution of Angiomax in 35 countries, including 12 countries in the European Union. We have also entered into a collaboration agreement with Grupo Ferrer Internacional for the registration, distribution and promotion of Angiomax in Spain, Portugal, Greece and eighteen Latin America markets including Argentina, Brazil and Mexico. We have entered into similar agreements with Medison Pharma Ltd. in Israel and Palestine and with CSL Limited in Australia.

Use of Angiomax in the Operating Room

Heparin is used widely as a procedural anticoagulant in major surgical procedures. Heparin is often unpredictable in its effect in these patients and frequently must be reversed with a protamine, a reversal agent. In addition, many surgery patients develop antibodies to heparin partly as a result of their exposure to heparin.

Based on hospital reimbursement data, in the United States in 2000 there were approximately 1,350,000 patients undergoing major cardiac or vascular surgical procedures, including 520,000 patients undergoing CABG and 347,000 patients undergoing vascular bypass surgery.

We have initiated a 100 patient Phase 2 trial of Angiomax comparing Angiomax to heparin in patients undergoing off pump CABG. The trial was initiated in November 2000 and 90 patients had been enrolled in the trial as of March 15, 2002. We plan to commence a Phase 3 trial program to study the use of Angiomax in HIT/HITTS patients undergoing CABG, with and without the use of a bypass pump.

Use of Angiomax in Acute Coronary Syndromes

Ischemic heart disease patients are subject to severe episodes often resulting in hospitalization that range from unstable angina to acute myocardial infarction. These severe episodes are collectively referred to as acute coronary syndromes.

Unstable angina is a condition in which patients experience the new onset of severe chest pain, increasingly frequent chest pain or chest pain that occurs while they are resting. Unstable angina is caused most often by a rupture of plaque on an arterial wall that ultimately decreases coronary blood flow but does not cause complete blockage of the artery. Unstable angina is often treated in hospitals with anticoagulation therapy that may include aspirin, indirect thrombin inhibitors such as heparin or low molecular weight heparin and GP IIb/IIIa inhibitors. Many unstable angina patients undergo angioplasty or CABG.

Acute myocardial infarction, or AMI, is a leading cause of death. AMI occurs when coronary arteries, which supply blood to the heart, become completely blocked by a clot. AMI patients are routinely treated with heparin, with and without fibrinolytics. Heart attack patients are increasingly undergoing angioplasty as a primary treatment to unblock clogged arteries.

Based on hospital reimbursement data, in the United States in 2000 there were approximately 1,882,000 patients hospitalized for acute coronary syndromes,

including 900,000 unstable angina patients and 982,000 patients with heart attacks of varying severity.

Angiomax Clinical Experience in AMI. We and Biogen have conducted clinical trials comparing Angiomax and heparin in over 17,600 AMI patients. Three Phase 2 trials demonstrated that use of Angiomax resulted in normal blood flow in at least 34% more patients than heparin and resulted in substantially less bleeding and the need for fewer transfusions than heparin.

In 2001, we completed a 17,000 patient Phase 3 clinical trial in AMI in 46 countries. In this Phase 3 trial, which we refer to as the HERO-2 trial, AMI patients received Angiomax or heparin prior to treatment with a fibrinolytic. All patients received aspirin and Streptase, a fibrinolytic. Two previous trials using high doses of hirudin in patients including heart attack patients had been stopped early because of excessive bleeding in the hirudin patients. Clinical results were assessed 30 days after treatment or in the hospital. The trial assessed second heart attacks, or reinfarction, based on both adjudication by a panel of experts and direct observation by the sites in the trial. In comparison to heparin-treated patients in the trials, Angiomax-treated patients experienced:

- no significant difference in mortality, the primary endpoint of the trial;
- 22% fewer second heart attacks; and
- no significant difference in hemorrhagic stroke and transfusions.

The following table summarizes the results for all patients in the HERO-2 trial.

	ANGIOMAX	HEPARIN	P-VAL
Number of patients	8,516	8,557	
At 30 days			
Death	10.5%	10.9%	0.44
In hospital			
Adjudicated reinfarction	2.8%	3.6%	0.00
Site determined reinfarction	3.5%	4.5%	0.00
Hemorrhagic stroke	0.6%	0.4%	0.0
Transfusions	1.4%	1.1%	0.1

Higher rates of bleeding in the Angiomax patients in the trial resulted in part from higher administered levels of anticoagulation in the Angiomax patients. When the data were adjusted for the level of anticoagulation, Angiomax patients experienced lower severe bleeding rates than the heparin patients.

Angiomax Clinical Experience in Unstable Angina. We and Biogen have completed five Phase 2 trials of Angiomax in patients with unstable angina or who had experienced a less serious form of MI known as non Q-wave MI. These trials enrolled a total of 630 patients, of whom 553 received various doses of Angiomax. These studies have demonstrated that Angiomax is an anticoagulant which can be administered safely in patients with unstable angina.

The largest of these Phase 2 trials was a multicenter, double blind, placebo-controlled and randomized study in 410 patients with unstable angina or

who had experienced non Q-wave MI. The trial compared the effect of three active dose levels and one placebo dose level of Angiomax with respect to death, MI, recurrent angina and major bleeding. Angiomax demonstrated a significant correlation between dose and anticoagulant effect.

In comparison to 160 patients treated with placebo doses in the trial, 250 patients treated with active doses of Angiomax experienced:

- a 68% reduction in death or MI in hospital with a p-value equal to 0.009; and

- a 59% reduction in death or MI after six weeks with a p-value equal to 0.014.

Biogen commenced a Phase 3 trial in 1994, the TIMI-8 trial, in unstable angina patients comparing Angiomax to heparin. The trial was discontinued after enrolling 133 patients when Biogen discontinued the Angiomax development program. Analysis of the data from the discontinued study showed the combined incidence of death, MI, or major bleeding reported in hospital within fourteen days of admission was 2.9% in Angiomax patients and 13.8% in heparin patients with a p-value of 0.03.

We have plans to commence a randomized Phase 3 trial program to study the use of Angiomax in emergency patients for whom angioplasty is planned and who are at high risk due to a heart attack or unstable angina.

Other Indications

We and Biogen have conducted a number of additional clinical trials of Angiomax for other indications.

HIT/HITTS. Approximately one to three percent of patients who have received heparin for seven to 14 days experience a condition known as HIT/HITTS. The underlying mechanism for the condition appears to be an immunological response to a complex formed by heparin and another factor, resulting in the lowering of platelet counts, commonly referred to as thrombocytopenia, and in some cases in arterial or venous clotting, which may

result in death or the need for limb amputation. Because further administration of heparin is not possible, an alternative anticoagulant is necessary.

Prior to 1997, Angiomax was administered to a total of 39 HIT/HITTS patients undergoing angioplasty requiring anticoagulation for invasive coronary procedures or treatment of thrombosis. For those patients undergoing angioplasty and other procedures, Angiomax provided adequate anticoagulation, was well-tolerated and rarely resulted in bleeding complications.

Based upon the encouraging data in the 39 patients previously treated, we are currently enrolling patients in a Phase 3 trial designed to evaluate the use of Angiomax for treatment of HIT/HITTS patients undergoing angioplasty. As of March 15, 2002, the trial had enrolled 27 patients and planned to enroll 50 patients in total. We plan to commence a Phase 3 trial program in HIT/HITTS patients undergoing CABG, with and without the use of a bypass pump.

Antithrombin-III deficiency. Heparin can only bind to thrombin by first binding to a blood factor called AT-III, which may be absent or present in insufficient amounts in some patients. AT-III deficiency is often severe or unpredictable in infants and children, making cardiovascular surgery and other procedures especially difficult. We plan to commence a Phase 2 trial program in prematurely

born babies with active thrombosis.

Deep Venous Thrombosis. Thirty-one patients with clots in the veins in their legs and 222 patients undergoing orthopedic surgical procedures were treated with Angiomax in two open-label, dose-ranging Phase 2 trials in 1990. Both studies established that Angiomax was an active and well-tolerated anticoagulant and that the anticoagulant effects correlated with the dose of Angiomax.

Regulatory Status

In December 2000, we received approval from the FDA for the use of Angiomax in combination with aspirin in patients with unstable angina undergoing coronary balloon angioplasty. In connection with this approval, the FDA has required us to complete our ongoing trial evaluating the use of Angiomax for the treatment of HIT/HITTS patients undergoing angioplasty. Angiomax is intended for use with aspirin and has been studied only in patients also receiving aspirin. We have received approval to market Angiomax stored at controlled room temperature as well as at refrigerated temperatures, which allows stocking of Angiomax in cardiac catheterization laboratories and other parts of a hospital that do not have refrigerators.

In February 1998, we submitted a Marketing Authorization Application, or MAA, to the European Agency for the Evaluation of Medicinal Products, or EMEA, for use in unstable angina patients undergoing angioplasty. Following extended interaction with European regulatory authorities, the Committee of Proprietary Medicinal Products, or CPMP, of the EMEA voted in October 1999 not to recommend Angiomax for approval in angioplasty. The United Kingdom and Ireland dissented from this decision. We have withdrawn our application to the EMEA and plan to resubmit an MAA with the results of the REPLACE-2 program if positive.

Angiomax was approved in New Zealand in September 1999 for use as an anticoagulant in patients undergoing angioplasty, and we began selling Angiomax in New Zealand in June 2000. We have submitted an application in Canada and Israel to market Angiomax for use in unstable angina patients undergoing angioplasty and are in active dialogue with Canadian and Israeli regulators. During 2002, we plan to file applications for marketing authorization in angioplasty in Australia and in several Latin American countries including Brazil and Mexico.

CLEVIDIPINE

In March 2002, we entered into a study and exclusive option agreement with AstraZeneca AB relating to the licensing, development and commercialization of clevidipine, an intravenous compound for the short term control of high blood pressure, for which Phase 3 clinical trials are planned. Blood pressure control is frequently important in patients undergoing surgery or other interventional procedures in hospital. These patients are often treated with multiple medications, which tends to increase the duration of the patient's stay in the intensive care units. We plan to investigate the potential of clevidipine to simplify and improve the treatment of these patients.

Clevidipine belongs to a well-known class of drugs called calcium channel inhibitors which are used to reduce high blood pressure. Clevidipine acts by selectively relaxing the smooth muscle cells that line small arteries, resulting in widening of the artery opening, and reduction of blood pressure within the artery. Unlike some other blood pressure reducing agents, including some other calcium channel inhibitors, clevidipine does not appear, based on animal studies, to have effects on muscles of the heart or the veins, has not been associated with quickening of the heart rate, and has been shown to improve

the pumping performance of the heart.

Prior to our acquisition of Clevidipine, AstraZeneca conducted Phase 2 clinical trials of clevidipine. These clinical trials demonstrated that clevidipine acts to reduce blood pressure almost immediately after intravenous infusion. Clevidipine is metabolized rapidly by enzymes in the blood, which results in the drug being cleared from the blood stream in a short period of time. Therefore the effects of clevidipine are short-lived, and in clinical trials it has been possible to demonstrate reductions in blood pressure that are dose-dependent and that cease rapidly after stopping clevidipine infusions.

In double-blind placebo controlled trials among patients undergoing cardiac surgery, clevidipine has been shown to cause a significant reduction in blood pressure. The following table summarizes the results of the largest clinical trial of clevidipine to date.

TABLE: COMPARISON OF CLEVIDIPINE WITH PLACEBO FOR REDUCTION IN BLOOD PRESSURE AMONG 91 PATIENTS UNDERGOING CARDIAC SURGERY

CLEVIDIPINE DOSE MICROGRAMS/KILOGRAM/ MINUTE VS. PLACEBO	TOTAL PATIENTS	NUMBER OF RESPONDERS (%) YES	NO	P-VALUE
Placebo	11	0 (0)	11 (100)	0.50
0.05	11	1 (9)	10 (91)	0.067
0.18	13	4 (31)	9 (69)	0.067
0.32	10	6 (60)	4 (40)	0.004
1.37	12	9 (75)	3 (25)	(Less than) 0.001
3.19	20	19 (95)	1 (5)	(Less than) 0.001
9.58	14	14 (100)	0 (0)	(Less than) 0.001

We believe that attributes of clevidipine demonstrated in clinical trials to date, namely rapid, titratable onset of effect on blood pressure, simple preparation and administration, arterial selectivity and rapid metabolism and elimination, could potentially benefit patients with high blood pressure undergoing surgical procedures and patients with severely elevated blood pressure that requires rapid reduction.

We expect to commence Phase 3 studies of clevidipine in these clinical situations in 2002. We plan to study clevidipine in patients undergoing CABG. We believe that clevidipine can be efficiently sold by our hospital sales force to hospital customers, including Angiomax customers, when and if clevidipine is approved for sale by the FDA and corresponding foreign regulatory authorities.

CTV-05

In 1999, we acquired from GyneLogix, Inc. exclusive worldwide rights to CTV-05, a strain of bacteria under clinical investigation for a broad range of applications in the areas of gynecological and reproductive health. We entered into a clinical trial agreement with the National Institutes of Allergy and Infectious Diseases, a division of the National Institutes of Health, commonly referred to as NIH, to conduct a Phase 2 trial of CTV-05, a proprietary biotherapeutic agent for the treatment of bacterial vaginosis, or BV. BV, the most common gynecological infection in women of childbearing age, is an imbalance of naturally occurring organisms in the vagina.

BV develops when certain bacteria normally present in the vagina in low levels multiply to infectious levels. BV is associated with serious health risks such as pelvic inflammatory disease, pre-term birth, post-surgical infection and an increased susceptibility to sexually transmitted diseases, including AIDS. The standard treatments currently prescribed for BV are oral or topical antibiotics including metronidazole and clindamycin. These treatments are not optimal, having significant recurrence rates. Moreover, antibiotic use depletes a beneficial bacteria called lactobacilli.

A healthy vagina is principally populated by lactobacilli. The presence of lactobacilli in the vagina, particularly those that produce hydrogen peroxide, has been linked to decreased incidence of BV and other urinary tract and gynecological infections. However, many women lack sufficient populations of hydrogen peroxide-producing lactobacilli to maintain vaginal health, making them more susceptible to infection. Studies had shown that the CTV-05 strain of lactobacillus is able to restore the natural balance of the bacteria in the vagina and produce both hydrogen peroxide and lactic acid, substances which are active against disease-causing bacteria and serve a protective role.

In the Phase 2 safety and efficacy trial, which we recently announced, CTV-05 was administered topically to BV patients. In the trial, treatment with CTV-05 resulted in vaginal colonization by lactobacillus crispatus in 62% of patients at 30 days compared to 2% on placebo (p-value