GENOME THERAPEUTICS CORP
Form 10-K
March 05, 2004

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

(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, 2003

OR

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

Commission file number: 0-10824

GENOME THERAPEUTICS CORP.

(Exact name of registrant as specified in its charter)

Massachusetts	**04-2297484**

(State or other jurisdiction of incorporation or organization)	(IRS employer identification number)
100 Beaver Street, Waltham, Massachusetts **(Address of principal executive offices)**	**02453** **(Zip Code)**

Registrant s telephone number: (781) 398-2300

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

None

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

Common Stock, $.10 Par Value

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 ¨

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

The aggregate market value of the voting and non-voting common equity held by non-affiliates as of June 27, 2003, the last business day of the registrant s most recently completed second fiscal quarter, was approximately $68,969,000.

The number of shares outstanding of the registrant s common stock as of March 3, 2004 was 73,894,560.

Documents Incorporated By Reference. Portions of the registrant s proxy statement for use at its Annual Meeting to be held on April 13, 2004 are incorporated by reference into Part III.

PART I

Item 1. ***Business***

Overview

We are a biopharmaceutical company committed to the clinical development and commercialization of new therapeutics to serve unmet medical needs. On February 6, 2004, we announced the completion of our merger with GeneSoft Pharmaceuticals, Inc. (Genesoft), a privately-held pharmaceutical company based in South San Francisco, California.

Our product portfolio is now led by the FDA-approved fluoroquinolone antibiotic FACTIVE® (gemifloxacin mesylate) tablets, indicated for the treatment of community-acquired pneumonia of mild-to-moderate severity and acute bacterial exacerbations of chronic bronchitis.

In addition, we are developing a novel antibiotic candidate, Ramoplanin, which is currently in clinical trials for the prevention and treatment of serious hospital-acquired infections. Ramoplanin is in a Phase III trial for the prevention of bloodstream infections caused by vancomycin-resistant enterococci and in a Phase II trial for the treatment of *Clostridium difficile*-associated diarrhea.

Our preclinical development programs include an oral peptide deformylase inhibitor series for the potential treatment of respiratory tract infections as well as development of a FACTIVE intravenous formulation. We also have six pharmaceutical alliances focused on the development of novel therapeutics and diagnostics for chronic human diseases and certain infectious diseases. These alliances were formed in previous years based on our genomics drug discovery expertise. Our business strategy has shifted away from gene discovery and partnerships of this type to focus on the development and commercialization of our own products.

Business Strategy

Our strategy is to advance our existing product and clinical candidates while exploring options to supplement our pipeline with additional opportunities, through either in-licensing or acquisition.

Commercial Launch and Further Development of FACTIVE Tablets

Our primary business focus is the launch of FACTIVE tablets in the U.S. for treating community-acquired pneumonia of mild to moderate severity and acute bacterial exacerbations of chronic bronchitis. We are building a sales and marketing infrastructure to support commercialization and plan to pursue additional indications for FACTIVE, as well as new formulations of the product.

Clinical Development of Ramoplanin and Other Assets

We are also committed to the development of our novel antibiotic, Ramoplanin. We are advancing the clinical program of Ramoplanin through a Phase II trial for the treatment of *Clostridium difficile*-associated diarrhea and a Phase III trial for the prevention of bloodstream infections caused by vancomycin-resistant enterococci. Additionally, we are exploring avenues for advancing our preclinical oral peptide deformylase inhibitor program, most likely through a co-development partner.

Potential In-Licensing and Acquisition of Other Products and Product Candidates

As we have done over the past three years, we will continue to explore ways of expanding our existing product portfolio through the licensing and acquisition of complementary products and product candidates.

Pharmaceutical and Diagnostic Programs

We have ten ongoing product development programs. Led by our FDA-approved product, FACTIVE tablets, our portfolio also includes Ramoplanin, in a Phase III clinical trial for the prevention of bloodstream infections caused by VRE and a Phase II clinical trial for the treatment of *Clostridium difficile*-associated diarrhea (CDAD). Our preclinical pipeline consists of an oral peptide deformylase inhibitor series and a

FACTIVE intravenous formulation program. In addition, we have six alliances with pharmaceutical companies including AstraZeneca, bioMérieux, Schering-Plough and Wyeth. We also plan to supplement our product portfolio by pursuing additional indications and treatment regimens for FACTIVE tablets.

Infectious Diseases Market

Infectious diseases represent the second leading cause of death worldwide accounting for over 14 million deaths each year. Bacterial infections are the sixth leading cause of death in the U.S. Antibacterials represent the largest segment of the anti-infective market, with an estimated $27 billion in total worldwide sales.

The principal structural classes of antibiotics include beta-lactams, quinolones, macrolides, tetracyclines, aminoglycosides, glycopeptides and trimethoprim combinations. Penicillin, a member of the beta-lactam class, which also includes extended-spectrum penicillins, cephalosporins and carbapenems, was first developed in the 1940s. Nalidixic acid, the earliest member of the quinolone class, was discovered in the 1960s. Major advances were made in the 1970s with the development of new beta-lactams and in the 1980s with the development of new quinolones and macrolides.

Bacterial resistance to existing antibiotics has been increasing in recent years, leading to bacterial infection recurrences, treatment failures and higher costs. These factors have fueled a growing need for more effective products in existing antibiotic classes, as well as for products with new mechanisms of action.

Community Respiratory Diseases (FACTIVE Tablets)

Acute Bacterial Exacerbations of Chronic Bronchitis: Chronic bronchitis is a health problem associated with significant morbidity and mortality. It is estimated that chronic bronchitis affects up to 13 million individuals or approximately 4% to 6% of adults in the United States. Patients with chronic bronchitis are prone to frequent exacerbations, characterized by increased cough and other symptoms of respiratory distress. Longitudinal studies have estimated that 1 to 4 exacerbations occur each year in patients with chronic bronchitis, and such exacerbations are estimated to account for approximately 12 million physician visits per year in the U.S. Antibiotic therapy, the standard treatment for acute bacterial exacerbations of chronic bronchitis, or ABECB, is typically effective in reducing the course of illness for patients.

Community-Acquired Pneumonia: Community-acquired pneumonia, or CAP, is a common and serious illness in the United States. The 3 to 4 million reported cases per year of CAP result in approximately 10 million physician visits, 1 million hospitalizations, approximately 64 million days of restricted activity and 45,000 deaths annually. Antibiotics are the mainstay of treatment for most patients with pneumonia, and where possible, antibiotic treatment should be specific to the pathogen responsible for the infection and individualized. However, since the responsible pathogen is not identified in a high proportion of patients with CAP, physicians usually take an empiric approach to treatment in the first instances. Over the last decade, resistance to penicillin and macrolides has increased significantly, and in many cases, quinolones are now recommended as a first line of therapy due to their efficacy against a wide range of respiratory pathogens, including many antibiotic resistant strains. The most recent treatment guidelines from the Infectious Diseases Society of America recommend quinolones as a first line treatment for certain higher-risk patients with CAP.

FACTIVE Tablets

As a result of our merger with Genesoft Pharmaceuticals, which was completed in February 2004, we gained rights to market gemifloxacin in North America and most of Europe under the brand name FACTIVE (gemifloxacin mesylate) tablets. Gemifloxacin is a member of the fluoroquinolone class of antibiotics. In April 2003, FACTIVE tablets were approved by the FDA for the treatment of ABECB and CAP of mild to moderate severity. In July 2003, FACTIVE tablets were also approved to treat CAP caused by multi-drug resistant *Streptococcus pneumoniae*, or *S. pneumoniae*, a growing clinical concern. Multi-drug resistant *S. pneumoniae*, or MDRSP, is defined as *S. pneumoniae* resistant to two or more of the following antibiotics: penicillin, second-generation cephalosporins (such as cefuroxime), macrolides, tetracyclines, and trimethoprim/sulfamethoxazole. FACTIVE tablets are the only antimicrobial currently approved for this indication.

FACTIVE tablets have potent *in vitro* activity against a wide range of Gram-positive, Gram-negative and atypical pathogens, including key respiratory pathogens, such as *S. pneumoniae, Haemophilus influenzae* and *Moraxella catarrhalis.* FACTIVE tablets are bactericidal at clinically achievable concentrations. Gemifloxacin, the active ingredient in FACTIVE tablets, targets two enzymes in bacteria and has minimum inhibitory concentrations, or MICs, as low as 0.03 µg/ml for *S. pneumoniae*. FACTIVE tablets have been administered to 6,775 patients and have a good overall safety and tolerability profile comparable to other currently marketed antibiotics. FACTIVE tablets have been the subject of over 200 publications. Among the research published are data indicating the drug s ability to reduce the number of ABECB recurrences over a six-month period following treatment.

Within the antibiotic market, quinolones, a product class with close to $3 billion in annual sales in the U.S. in 2002, have been gaining market share at the expense of older antibiotics, according to IMS Health. This is a trend that is expected to continue as resistance to older antibiotic classes increases. Due to their microbiological activity and clinical efficacy, FACTIVE tablets represent an alternative choice for the treatment of certain respiratory tract infections.

Mechanism of Action: FACTIVE tablets act by inhibiting bacterial DNA synthesis through the inhibition of both DNA gyrase and topoisomerase IV, two enzymes essential for bacterial growth and survival. Strains of *S. pneumoniae* showing mutations in both DNA gyrase and topoisomerase IV (double mutants) are resistant to most fluoroquinolones. Since gemifloxacin has the ability to inhibit both target enzymes at therapeutically relevant drug levels, some of these *S. pneumoniae* double mutants remain susceptible to FACTIVE tablets. FACTIVE tablets are also active against many strains of *S. pneumoniae* that are resistant to other classes of antibiotics. There is no known bacterial cross-resistance between gemifloxacin and any other class of antimicrobials.

Clinical Efficacy: The clinical program for FACTIVE tablets included 14 Phase III trials. FACTIVE tablets were studied for the treatment of acute bacterial exacerbation of chronic bronchitis in three pivotal, double-blind, randomized, active-controlled clinical trials using 320 mg once daily for 5 days. In these non-inferiority studies, a total of 826 patients received treatment with FACTIVE tablets and 822 patients received treatment with an active comparator, namely levofloxacin, clarithromycin or amoxicillin/clavulanate. The primary endpoint was clinical response at follow-up. The results for the principal Phase III ABECB studies demonstrated that FACTIVE tablets given once daily for 5 days were at least as effective as the comparators given for 7 days. The clinical success rates for each of these three trials were as follows:

FACTIVE tablets 5 days (320 mg): 88.2%	Levofloxacin 7 days (500 mg): 85.1%
FACTIVE tablets 5 days (320 mg): 86.0%	Clarithromycin 7 days (500 mg 2 times/day, or bid): 84.8%
FACTIVE tablets 5 days (320 mg): 93.6%	Amoxicillin/clavulanate 7 days (500 mg/125 mg, 3 times/day, or tid): 93.2%

FACTIVE tablets were also studied for the treatment of community-acquired pneumonia in three double-blind, randomized, active-controlled clinical studies, one open, active-controlled study, and two uncontrolled studies. In total, 1,349 patients with CAP were treated with FACTIVE tablets, including 1,037 patients treated for 7 days and 927 patients were treated with an active comparator. The primary endpoint for each of these three trials was clinical response at follow-up.

The results of these studies showed that gemifloxacin was effective in the treatment of mild to moderate CAP. The clinical success rates for FACTIVE tablets in studies with a fixed 7-day duration ranged from 89% to 92%. In the pivotal CAP comparator study, a 7-day treatment regimen of FACTIVE tablets 320 mg once daily was shown to be as effective as a 10-day treatment course of amoxicillin/clavulanate (500 mg/125 mg tid). The clinical success rates for the two treatment arms were:

FACTIVE tablets 7 days (320 mg): 88.7%	Amoxicillin/clavulanate 10 days (500 mg/125 mg tid): 87.6%

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Clinical studies showed that FACTIVE tablets were effective in the treatment of CAP due to penicillin-resistant *S. pneumoniae*, or PRSP. Of 11 patients with PRSP treated with FACTIVE tablets for 7 days, 100% achieved both clinical and bacteriological success at follow-up. FACTIVE tablets are also effective in the treatment of CAP due to MDRSP. In clinical trials, of 22 patients with MDRSP treated with FACTIVE tablets for 7 days, 19 (87%) achieved both clinical and bacteriological success at follow-up. FACTIVE tablets are the first and only antibiotic approved to treat mild to moderate CAP caused by this multi-drug resistant organism.

Potential Competitive Advantages: The potential competitive advantages of FACTIVE tablets include:

- FACTIVE tablets have been shown in *in vitro* studies to be active against many bacterial isolates resistant to other classes of antibiotics, and are the only antibiotic approved to treat community-acquired pneumonia of mild to moderate severity caused by multi-drug resistant *S. pneumoniae.*

- FACTIVE tablets have a dual mechanism of action in bacteria, which targets two enzymes essential for bacterial growth and survival at therapeutically relevant drug levels, and as a result we believe have low *in vitro* potential for resistance generation.

- FACTIVE tablets can be dosed once daily, with short courses of therapy for both ABECB (5 days) and CAP (7 days).

- FACTIVE tablets have patent protection into 2015, longer than any currently marketed fluoroquinolones or other antibiotics widely used to treat respiratory tract infections.

Safety and Tolerability: FACTIVE tablets have been studied in nearly 7,000 patients and have a favorable safety profile. The incidence of adverse events reported for FACTIVE tablets was low and comparable to comparator drugs, namely beta-lactam antibiotics, macrolides and other fluoroquinolones. Most adverse events were described as mild to moderate.

Although rash was more frequent among FACTIVE-treated patients in the total patient population than among those who received comparator drugs, in the adult population most at risk for CAP of mild to moderate severity and ABECB (patients over 40 years of age) and at the approved dosage (320 mg for 7 days or less), the rate of rash with FACTIVE tablets was low and comparable to that seen with other antibiotics.

As a post-marketing study commitment, the FDA has required a prospective, randomized study comparing FACTIVE tablets (5,000 patients) to an active comparator (2,500 patients) in patients with CAP or ABECB. This study will include patients of different ethnicities, to gain safety information in populations not substantially represented in the existing clinical trial program, specifically as it relates to rash. Patients will be evaluated for clinical and microbiological success. This Phase IV trial is expected to commence proximate to the product launch in the U.S.

Additional Development of Gemifloxacin: Clinical trials of FACTIVE tablets for the treatment of acute bacterial sinusitis, or ABS, have also been completed. Two double-blind, randomized, active-controlled clinical studies were conducted to examine the efficacy of FACTIVE 320 mg once daily for 7 days in the treatment of patients with ABS. In these studies, 540 patients received FACTIVE tablets and 536 patients received active comparator, namely trovafloxacin or cefuroxime. The primary endpoint was clinical success at follow-up. The result of these clinical trials showed comparable clinical success for patients treated with FACTIVE tablets and those treated with comparator drugs. In addition, a double-blind, randomized, active-controlled clinical study comparing a FACTIVE 7-day treatment regimen for ABS with a FACTIVE 5-day treatment regimen showed similar efficacy between the two treatment arms. Two open-label studies also support the efficacy of FACTIVE tablets given for 5 days for the treatment of ABS. We anticipate filing a New Drug Application (NDA) for this indication in 2005.

An intravenous formulation of gemifloxacin is also in development. We expect that FACTIVE intravenous will undergo a Phase I bioequivalence study in the coming months. Pending a successful outcome of the first study, we plan to conduct a single Phase III trial of the intravenous formulation before pursuing market approval from the FDA. We are currently reviewing a strategy for filing for regulatory approval of FACTIVE tablets in the European Union and anticipate that these filings could be made as early as 2006.

License Agreement: We license the rights to gemifloxacin, the active ingredient in FACTIVE tablets, from LG Life Sciences of the Republic of Korea. We have the rights to commercialize gemifloxacin in North America, France, Germany, the United Kingdom, Luxembourg, Ireland, Italy, Spain, Portugal, Belgium, the Netherlands, Austria, Greece, Sweden, Denmark, Finland, Norway, Iceland, Switzerland, Andorra, Monaco, San Marino and Vatican City. The term of the agreement extends at least through gemifloxacin s patent life which currently expires in 2015 with respect to the principal patents for gemifloxacin, and the term could extend further depending upon several factors, including whether we obtain patent extensions and the timing of our commercial sale of the product in a particular country. The agreement also requires a minimum sales commitment over a period of time, which if not met, would result in the technology being returned to LG Life Sciences. Under this agreement, we are responsible, at our expense and through consultation with LG Life Sciences, for the clinical and commercial development of gemifloxacin in the countries covered by the license, including the conduct of clinical trials, the filing of drug approval applications with the FDA and other applicable regulatory authorities and the marketing, distribution and sale of gemifloxacin in our territory; provided, that LG Life Sciences has the right to co-promote the product, on terms to be negotiated, in our territory for 2008 and periods commencing thereafter, in which case our royalty obligations to LG Life Sciences would cease. The agreement also provides LG Life Sciences with the right to negotiate with us for 180 days to obtain rights to develop our DNA Nanobinder compounds in East Asia for certain skin disorders following the completion of a Phase II clinical trial for such a compound.

Under our license agreement, we were required to pay LG Life Sciences $8 million upon the completion of the merger with Genesoft and will have to make additional payments when specific commercialization milestones are achieved. In addition, per our agreement with LG Life Sciences, we have made the first half of a $4.8 million payment for the purchase of the drug inventory. The arrangement also provides for potential additional milestone payments to LG Life Sciences of up to $22 million, primarily upon achieving sales targets. We are required to buy bulk drug requirements from LG Life Sciences (see Manufacturing below), and will pay LG Life Sciences a royalty on sales in the U.S. and the territories covered by the license in Europe. The gross margin on product sales, including royalty obligations, is projected to be approximately 75% during the first two years, and in the 65 to 70% range after those periods.

Hospital-Acquired Infections (Ramoplanin)

Clostridium difficile-Associated Diarrhea (CDAD): CDAD, a serious form of colitis caused by toxins produced by the Gram-positive bacterium *Clostridium difficile* (*C. difficile*), is the most common form of antibiotic-associated diarrhea in the hospital setting. One study has demonstrated that as many as 20% of hospital patients are colonized with *C. difficile* either prior to or during admission. Because it is a spore-forming bacterium, *C. difficile* is readily spread from person to person, especially in the hospital and nursing home environment. Under certain conditions, such as extended antibiotic therapy and gastrointestinal surgery, *C. difficile* can colonize the gut and release toxins, leading to bowel inflammation and severe diarrhea. Serious cases can occur and involve the development of fulminant colitis (severe inflammation of the colon); such occurrences can be life threatening, especially in elderly or immunocompromised populations.

Over 400,000 patients are treated in U.S. hospitals each year for CDAD. CDAD is associated with an average increase of length of stay in the hospital of 3.6 days and an average increase in hospital costs of over $3,600 per patient. It is estimated that the annual increase in hospital costs attributable to CDAD exceeds $1 billion.

Current therapies for the treatment of CDAD include oral metronidazole and oral vancomycin. Both of these agents are associated with a 15-20% relapse rate. The use of oral vancomycin has been associated with the selection of vancomycin-resistant organisms, including vancomycin-resistant enterococci (VRE). Resistance has been reported for both drugs.

Enterococcal Bloodstream Infections: Enterococci are a family of Gram-positive bacteria that are part of the normal flora of the human gastrointestinal, or GI, tract. While these organisms do not normally cause infections in healthy people, they become a threat in patients that have a compromised immune system and are frequently found in hospitalized patients. Enterococci are the second most common cause of bloodstream infections acquired in the Intensive Care Units (ICUs) of hospitals in the United States. Enterococcal bloodstream infections in the ICU have been associated with a crude mortality rate of over 30%.

For thirty years, the antibiotic of last resort for enterococcal bloodstream infections was vancomycin. However, the widespread use of vancomycin and other antibiotics, such as third generation cephalosporins, has increased the prevalence of resistant strains of enterococci, known as vancomycin-resistant enterococci (VRE). In 2000, more than 26% of intensive care unit enterococci infections were caused by VRE, a 93% increase from 1994.

Given its rapid spread and the difficulty in treating the bloodstream infections it causes, VRE has received significant attention from both the medical and public health communities. Most VRE are not only resistant to vancomycin, but also to other common antibiotics. This resistance provides VRE with a selective advantage over other enterococcal isolates in the gut and enables resistant pathogens to easily colonize the human GI tract. The morbidity and mortality associated with VRE bloodstream infections is substantially higher than for enterococcal bloodstream infections caused by vancomycin-susceptible strains of enterococci.

Given the high morbidity, mortality and cost of VRE bloodstream infections and the limited treatment options for active infections, a great deal of focus within the infectious diseases community has been placed on infection control practices within the hospital to prevent VRE infections. Infection control measures to date have focused on screening for colonized patients and using barrier methods to avoid the spread of the bacteria to other patients. Typically, these measures require isolation of the patient in a room with negative air pressure and the gowning and gloving of physicians and nursing staff. Such patients are often not allowed to have family visitors.

The large quantity of VRE in the gut has motivated investigators to seek to decolonize the gut in an attempt to prevent VRE bloodstream infections. However, attempts to date to prevent VRE bloodstream infections by decolonization have been unsuccessful, according to an article in *The New England Journal of Medicine*. Bacitracin has been tried in combination with or without gentamicin or a tetracycline. Novobiocin has also been tried. It is believed that these approaches have not been successful due to lack of potency or the inability of the antibacterials to reach sufficient levels in the gut to suppress VRE effectively.

Ramoplanin

In October 2001, we in-licensed Ramoplanin from Vicuron Pharmaceuticals Inc. (Vicuron). Ramoplanin is a novel glycolipodepsipeptide antibiotic produced by fermentation of the bacteria *Actinoplanes*, with activity against Gram-positive aerobic and anaerobic microorganisms. In preclinical studies, Ramoplanin has been shown to be bactericidal against most Gram-positive species, including methicillin-resistant staphylococci, VRE and *C. difficile*. Ramoplanin inhibits the bacterial cell wall peptidoglycan biosynthesis with a mechanism different from that of vancomycin, teicoplanin or other cell wall-synthesis inhibitors. No evidence of cross-resistance between Ramoplanin and other glycopeptide antibiotics has been observed. Ramoplanin has a unique profile that may make it a particularly attractive compound for killing bacteria in the GI tract. As a result, we are studying the product candidate for the treatment of certain infections (such as *C. difficile*) that occur in the GI tract as well as the prevention of bloodstream infections by Gram-positive organisms that are concentrated in the GI tract, including VRE. Finally, Ramoplanin may show value in preventing patient-to-patient transmission of Gram-positive pathogens in the hospital setting.

Clinical Trials: In a Phase II, multicenter, double-blind, placebo-controlled trial examining suppression of GI VRE colonization, Ramoplanin was well tolerated. In addition, after seven days of treatment, 90% of patients who were colonized with VRE at the beginning of the study had no detectable VRE in their GI tract, while all of

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the placebo patients had detectable VRE (p=0.01). Subsequently, the ongoing Phase III study was designed to demonstrate whether oral Ramoplanin reduced the incidence of VRE bloodstream infections in cancer patients carrying VRE bacteria in their intestines. Ramoplanin has been granted Fast Track status by the FDA for this indication. This trial is on-going. Approximately half of the planned 950 patients have been enrolled in the study at more than 40 clinical trial sites in the U.S. and more than 60% of the projected 65 events (bloodstream infections caused by VRE) required for completion have been recorded. Enrollment in this study remains challenging due, in part, to many potential patients being excluded from the study because of their participation in other clinical trials to treat their underlying malignancies.

In 2003, we began a Phase II trial to assess the safety and efficacy of Ramoplanin to treat CDAD. The protocol calls for an 87-person, open-label, multi-center trial comparing two doses of Ramoplanin (200 mg and 400 mg twice daily) to vancomycin (which requires a dose of 125 mg four times daily for the treatment of CDAD). Both agents are administered for ten days, during which data on Ramoplanin is being collected to measure safety and efficacy. The results of the Phase II trial will guide the design of a Phase III investigation of Ramoplanin for the treatment of CDAD. Ramoplanin has demonstrated both *in vitro* and *in vivo* (hamster model) activity against *C. difficile,* including strains resistant to metronidazole and vancomycin. The clinical development program of Ramoplanin for the potential treatment of CDAD received Fast Track status from the FDA in February 2004. We currently expect to announce initial results for the Phase II trial of Ramoplanin for CDAD in the first half of 2004 and, assuming successful completion of this trial, commence the Phase III CDAD program before the end of 2004. Based on these development plans, we anticipate that we will file an NDA for the CDAD indication prior to filing one for the VRE bloodstream prevention claim.

Potential Competitive Advantages: The potential competitive advantages of Ramoplanin include:

- Ramoplanin is from a novel class of antibiotics and there have been no observed cases of bacterial resistance or cross-resistance with other antibiotics.
- Ramoplanin is orally administered, but not absorbed into the bloodstream, so it concentrates and exerts its killing effects in the GI tract.
- Its bactericidal effect may result in lower potential for bacteria to develop resistance.
- Ramoplanin has a Gram-positive spectrum of activity and low potency against Gram-negative anaerobes making it less likely that its use will result in the overgrowth of other opportunistic organisms.
- There are currently no products, to our knowledge, addressing the critical need for preventing VRE bloodstream infections.

License Agreement: Our license agreement with Vicuron provides us with exclusive rights to develop and market oral Ramoplanin in the U.S. and Canada. Under this agreement, we are responsible, at our expense, for the clinical and non-clinical development of Ramoplanin in our field, the prevention and treatment of human disease, in the United States and Canada, including the conduct of clinical trials and the filing of drug approval applications with the FDA and other applicable regulatory authorities. Vicuron is responsible for providing us with all information in its possession relating to Ramoplanin in our licensed field and for cooperating with us in obtaining regulatory approvals of Ramoplanin. We are obligated to purchase and Vicuron is obligated to provide the bulk material for the manufacture of the product. Under the terms of the agreement, we paid Vicuron initial consideration of $2 million. We will also make milestone payments of up to an additional $8 million in a combination of cash and notes convertible into our stock if certain development milestones are met. In addition to purchasing bulk material from Vicuron, we will pay a royalty to Vicuron on product sales. The combined total of bulk product purchases and royalties is expected to be 26% of our net product sales.

Drug Discovery Alliances

In the past, it was our business strategy to form strategic alliances with major pharmaceutical companies to discover, develop and commercialize products based on our gene discoveries. While we have shifted our focus away from forming alliances of this type and have discontinued our gene discovery activities, our six existing pharmaceutical alliances still have the potential to deliver value in the future.

Bacterial and Fungal Infection Alliances

Ulcers: Approximately two-thirds of the world s population is infected with *H. pylori* and 25 million Americans suffer from peptic ulcer disease at some point in their life. Worldwide sales of anti-ulcerants were $17.4 billion in 2000.

The pathogen, *H. pylori*, is believed to be responsible for 90% of duodenal ulcers, the most common type of ulcer, and approximately 80% of gastric peptic ulcers. It is estimated that those infected with H. pylori have a two to six fold increased likelihood of developing stomach cancer. Using our sequencing technology, we completed the sequencing and finishing of the genome of *H. pylori*. We believe that drugs targeted at genes essential to the survival of *H. pylori* may provide novel treatments for peptic ulcers.

In September 1995, we formed an alliance with AstraZeneca to identify genes critical to the survival of *H. pylori* and proteins on the surface of the bacterium that we believe to be likely targets for drugs. AstraZeneca is a leader in the field of products to treat peptic ulcer disease. Its anti-ulcer franchise, which includes Nexium® and Prilosec®, generated worldwide sales of $6.0 billion in 2003. As of December 31, 2003, we had received payments of $13.7 million under this alliance and have rights to receive, based on attainment of milestones, an additional $9.8 million of payments in addition to potential royalties. In August 1999, we completed our research obligations under this alliance and turned over validated drug targets and assays to AstraZeneca for preclinical testing. AstraZeneca announced in 2002 that it had begun optimization on a lead series identified through the high-throughput screening program conducted using one of these targets. On March 31, 2003, AstraZeneca s exclusive access rights to our *H. pylori* genomic sequence technology terminated.

Drug-Resistant Bacterial Infections: The pathogen *Staphylococcus aureus* (*S. aureus*) is a common cause of skin, wound and blood infections. *S. aureus* infections are typically treated with antibiotics. In recent decades, the incidence of *S. aureus* infections that are resistant to available antibiotic treatments has risen. Using our high-throughput sequencing capabilities, we have sequenced the genome of antibiotic-resistant *S. aureus*. We believe that drugs targeted at genes essential to the survival of *S. aureus* may provide novel treatments for skin, wound and blood infections contracted in hospitals.

In December 1995, we formed an alliance with Schering-Plough to identify and validate gene targets for the development of drugs to treat infections caused by *S. aureus* and other pathogens that have become resistant to current antibiotics. Schering-Plough is an established participant in the anti-infective market and a leader in the utilization of genomics to discover novel anti-infective products. As of December 31, 2003, we had received payments of $21.5 million under this alliance and have rights to receive, based on attainment of milestones, an additional $24.0 million of payments as well as potential royalties. As of December 31, 2001, we had completed our research obligations under this alliance and had turned over validated drug targets and assays to Schering-Plough for high-throughput screening.

Fungal Infections: The past twenty years have seen dramatic changes in the pattern of fungal infections in humans. These pathogens are of concern because of their increasing incidence in immunocompromised patients, such as AIDS patients, transplant recipients, cancer patients and other groups of immunocompromised individuals. Increased international travel and misuse of antimicrobial agents have also contributed to the emerging resistance to certain treatments. Industry sources estimate that the global market for prescription antifungal drugs was approximately

$4.3 billion in 2002, with non-prescription fungal treatments adding

significantly to overall market size. Currently, there are a limited number of antifungals available for use against hospital related fungal infections, and many of the products currently on the market have serious side effects. We believe that drugs targeted at genes that are essential to the survival of fungal pathogens may represent novel and effective treatments for fungal infections.

In September 1997, we formed an alliance with Schering-Plough to use our high-throughput sequencing capabilities and genomic tools to identify new, validated fungal targets for the development of drugs to treat fungal infections. Schering-Plough is a leader in the field of drugs targeted against fungal infections, with market leading products such as the Lotrimin AF® and Tinactin® lines of topical antifungals. As of December 31, 2003, we had received payments of $12.2 million under this alliance and have rights to receive, based on attainment of milestones, an additional $21.0 million of payments in addition to potential royalties. In early 2002, we completed our research obligations under this alliance and turned over validated drug targets and assays to Schering-Plough for high-throughput screening.

Infectious Disease Diagnostics: The World Health Organization estimates that more than 14 million people worldwide die of an infectious disease each year, with many of those infections acquired in hospitals. There has been a global resurgence of infectious diseases, including the identification of new pathogens, the re-emergence of old infectious agents and the rapid development of resistance to anti-infective agents. Rapidly identifying the specific microorganisms involved in a disease is becoming increasingly important and complex, providing challenges and opportunities for infectious disease testing. Highly sophisticated and versatile methods are needed to identify a larger and more diverse list of pathogens, including variants with drug-resistant characteristics. It is anticipated that nucleic acid tests incorporating such methods will be part of the fastest growing segment of the $28.5 billion *in vitro* diagnostic global market.

In September 1999, we entered into a strategic alliance with bioMérieux to develop, manufacture and sell *in vitro* pathogen diagnostics for human clinical and industrial applications. A privately held company based in France, bioMérieux is one of the top 10 diagnostics companies in the world and a leader in the field of microbiology. The total amount of research and development funding provided by bioMérieux approximated $5.2 million for the four-year term of the agreement, which concluded on December 31, 2003. As of December 31, 2003, we had received payments of $5.2 million and have rights to receive future milestone payments and royalties based upon successful commercialization of diagnostic products.

Chronic Human Disease Alliances

Osteoporosis: Osteoporosis is a major health problem characterized by low bone mass that affects more than 200 million people worldwide and approximately one-third of post-menopausal women. In the U.S. alone, osteoporosis contributes to more than 1.5 million bone fractures per year. Estimated direct expenditures in the United States for osteoporosis and associated fractures were $17.0 billion in 2001. Twin and family studies suggest a strong genetic component to the disease. Under a collaboration with Creighton University of Omaha, Nebraska, we gained access to data from related individuals identified by Creighton who exhibit high bone mass. We believe the identification of genes regulating bone density and disease progression may lead to the discovery of novel drugs for treating osteoporosis by increasing bone mass, as well as to the development of diagnostic tests.

In December 1999, we formed an alliance with Wyeth to develop drugs to treat osteoporosis based on our genetic research. Wyeth is a leader in the field of women s health with a broad array of products. As of December 31, 2003, we had received payments of $10.3 million under this alliance and have rights to receive, subject to the achievement of milestones, an additional $108.7 million in milestone payments and research support, as well as royalties on sales of any products developed. This program entered high-throughput screening for drug candidates in 2002. As of December 31, 2003, we had completed our research requirements under this agreement.

Asthma: Asthma affects between 100 and 150 million people worldwide according to the World Health Organization and the incidence of asthma appears to be rising dramatically. In the United States, asthma now affects approximately 4% to 10% of the United States population.

The annual direct and indirect costs associated

with treating the disease close to $15.0 billion. Published research suggests that multiple genetic factors, as well as environmental influences, play a role in the disease. We believe that the asthma genes that we have identified will facilitate the development of superior diagnostics and novel drugs.

In December 1996, we formed an alliance with Schering-Plough to use our disease gene identification strategies to identify genes involved in the development of asthma. Schering-Plough is a leader in the field of allergy and respiratory care products, with products such as Clarinex® and the Claritin® line of antihistamines; Schering-Plough s allergy and respiratory franchise reported sales of $2.4 billion in 2003. As of December 31, 2003, we had received payments of $42.5 million under this alliance and have rights to receive, based on attainment of milestones, an additional $38.5 million of payments as well as potential royalties. Under this alliance, we used our proprietary genomics tools, bioinformatics and high-throughput sequencing to discover two genes associated with asthma. As of December 31, 2002, we had completed our research obligations under this alliance. The two genes discovered have been transferred to Schering-Plough for further drug discovery efforts and the program is now in high-throughput screening for drug candidates.

Bone Diseases: On January 9, 2004, we announced the completion of our research alliance with Amgen for the identification and development of novel therapeutic agents for bone diseases, including osteoporosis. During the collaboration, we discovered a novel gene linked to high bone mass. Upon termination, we regained intellectual property rights to the program and the gene discovery. We received $4.7 million in revenue associated with this alliance during the year ended December 31, 2003.

Internal Drug Discovery

Bacterial Infections

Our current portfolio of internal drug discovery programs focuses on bacterial infections and the growing need to develop antibacterial compounds with novel mechanisms of action.

Peptide Deformylase Inhibitors: In August 2002, Genesoft entered into a research and license agreement with British Biotech Pharmaceuticals Ltd., now Vernalis, to co-develop inhibitors of peptide deformylase, or PDF, a novel iron-binding enzyme essential for bacterial growth but not involved in human cytoplasmic protein synthesis. Genome Therapeutics believes that PDF inhibitors represent an excellent opportunity for the development of novel mode of action antibiotics.

Preclinical studies of our first-generation PDF inhibitor indicated that the compound may have potential for the treatment of hospitalized patients suffering from CAP. An intravenous formulation of this compound entered Phase I clinical trials in October 2002. The drug candidate was well tolerated and demonstrated good pharmacokinetic properties, but did not have an ideal spectrum of activity against common respiratory pathogens. Our research program is now focused on the optimization of second-generation, orally-available PDF inhibitors with the potential to target the broader community-based antibiotic market. Several compounds have been identified with improved properties, including good activity against *H. influenzae.* With continued success, we anticipate selecting a development candidate and initiating IND-enabling studies.

Novel Anti-Infective Series: As a result of our internal drug discovery efforts, we have identified two novel chemical series ready to enter the lead optimization phase with a partner. These two lead series are aimed at novel, broad-spectrum targets and have the potential to be new classes of antibacterials. In addition to these lead compounds, we have identified hit series on six additional antimicrobial screens.

Genomics Services

As part of our continued evolution into a focused biopharmaceutical company, in March 2003 we sold our genomics services business to privately held Agencourt Bioscience Corporation (Agencourt). As part of the agreement, we transferred our sequencing operations, including certain equipment and personnel to Agencourt. We received an upfront cash payment of $200,000 and shares of Agencourt common stock and we will receive a percentage of revenues from commercial and government customers that were transferred to Agencourt for a period of two years from the date of the agreement.

The PathoGenome Database, a database consisting of proprietary and publicly available genetic information from over thirty microbial organisms, including organisms responsible for the most prevalent bacterial infections has, since 2001, been marketed, maintained and distributed by EraGen Biosciences. We retain our rights to use it and receive a percentage of subscription fees and royalties from subscriber discoveries, but we do not expect that this program will have a significant impact on our business moving forward.

Patents and Proprietary Technology

Our commercial success depends in part on our ability to obtain intellectual property protection on our methods, technologies and discoveries. To that end, our policy is to protect our proprietary technology primarily through patents.

We currently own or license approximately 50 issued U.S. patents, approximately 127 pending U.S. patent applications, 50 issued foreign patents and approximately 143 pending foreign patent applications. These patents and patent applications primarily relate to (1) the field of human and pathogen genetics, (2) the chemical composition, use, and method of manufacturing FACTIVE tablets, (3) metalloenzyme inhibitors, their uses, and their targets, and (4) DNA-Nanobinder compounds and their use as anti-infective therapeutics. Our material patents are as follows:

U.S. Patent No. 5,633,262 granted May 27, 1997, relating to quinoline carboxylic acid derivatives having 7-(4-amino-methyl-3-oxime) pyrrolidine substituent; licensed from LG Life Sciences; expiring June 15, 2015

U.S. Patent No. 5,776,944 granted July 7, 1998, relating to 7-(4-aminomethyl-3-methyloxyiminopyrroplidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid; licensed from LG Life Sciences; expiring June 15, 2015

U.S. Patent No. 5,869,670 granted February 9, 1999, relating to 7-(4-aminomethyl-3-methyloxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid; licensed from LG Life Sciences; expiring June 15, 2015

U.S. Patent No. 5,962,468 granted October 5, 1999, relating to 7-(4-aminomethyl-3-methyloxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid; licensed from LG Life Sciences; expiring June 15, 2015

U.S. Patent No. 6,340,689 granted January 22, 2002, relating to methods of using quinolone compounds against atypical upper respiratory pathogenic bacteria; licensed from LG Life Sciences; expiring September 14, 2019

U.S. Patent No. 6,262,071 granted July 17, 2001, relating to methods of using antimicrobial compounds against pathogenic Mycoplasma bacteria; licensed from LG Life Sciences; expiring September 21, 2019

U.S. Patent No. 6,331,550 granted December 18, 2001, relating to methods of using of quinolone compounds against anaerobic pathogenic bacteria; licensed from LG Life Sciences; expiring September 21, 2019

U.S. Patent No. 6,455,540 granted September 24, 2002, relating to methods of Use of quinolone compounds against anaerobic pathogenic bacteria; licensed from LG Life Sciences; expiring September 21, 2019

U.S. Patent No. 6,423,690 granted July 23, 2002, relating to antibacterial agents; licensed from Vernalis; expiring February 5, 2019

U.S. Patent No. 6,441,042 granted August 27, 2002, relating to hydroxamic acid derivatives as antibacterials; licensed from Vernalis; expiring May 14, 2019

U.S. Patent No. 6,380,370 granted April 30, 2002, relating to *Staphylococcus epidermidis*; expiring August 13, 2018

U.S. Patent No. 6,551,795 granted April 22, 2003, relating to *Pseudomonas aeruginosa*; expiring February 18, 2019

U.S. Patent No. 6,562,958 granted May 13, 2003, relating to *Acinetobacter baumannii*; expiring June 4, 2019

U.S. Patent No. 6,583,275 granted June 24, 2003, relating to *Enterococcus faecium*; expiring June 30, 2018

U.S. Patent No. 6,583,266 granted June 24, 2003, relating to *Mycobacterium tuberculosis* and *leprae*; expiring June 24, 2020

U.S. Patent No. 6,605,709 granted August 12, 2003, relating to *Proteus mirabilis*; expiring April 5, 2020

U.S. Patent No. 6,6105,836 granted August 26, 2003, relating to *Klebsiella pneumoniae*; expiring January 27, 2020

U.S. Patent No. 6,617,156 granted September 9, 2003, relating to *Enterococcus faecalis*; expiring August 13, 2018

While it is difficult to assess the value of our intellectual property portfolio, the patents named above may provide a competitive advantage in certain instances in the pathogen and anti-infective field by requiring others to obtain a license from us if they wish to produce competing products.

Under our license agreement with LG Life Sciences, we obtained an exclusive license to develop and market gemifloxacin in certain territories. This license covers 11 issued U.S. patents and a broad portfolio of corresponding foreign patents and pending patent applications. These patents include claims that relate to the chemical composition of FACTIVE tablets, methods of manufacturing and their use for the prophylaxis and treatment of bacterial infections. The U.S. patents are currently set to expire at various dates, ranging from 2015, in the case of the principal patents relating to FACTIVE tablets, to 2019. We have filed patent term extension applications, covering the regulatory review process, for the principal patents. If granted, these extensions would extend the exclusivity period through 2017. We also have the exclusive right to use FACTIVE trademarks, trade names, domain names and logos in conjunction with the use or sale of the product in the territories covered by the license.

LG Life Sciences has the obligation under the agreement to diligently maintain its patents and the patents of third parties to which it has rights that, in each case, relate to gemifloxacin, the active ingredient in FACTIVE tablets. We have the right, at our expense, to control any litigation relating to suits brought by a third party alleging that the manufacture, use or sale of gemifloxacin in its licensed field in the territories covered by the license infringes upon our rights. We also have the primary right to pursue actions for infringement of any patent licensed from LG Life Sciences under the license agreement within the territories covered by the license. If we elect not to pursue any infringement action, LG Life Sciences has the right to pursue it. The costs of any infringement actions are first paid out of any damages recovered. If we are the plaintiff, the remainder of the damages are retained by us, subject to our royalty obligations to LG Life Sciences. If LG Life Sciences is the plaintiff, the remainder of the damages are divided evenly between us and LG Life Sciences, subject to our royalty obligations to LG Life Sciences.

LG Life Sciences, as owner of U.S. Patent Nos. 5,776,944 and 5,962,468, submitted requests for reexamination to the U.S. Patent & Trademark Office, or PTO, in order to place additional references into the record of each patent. Both requests were granted by the PTO. Patent 468 has been reexamined with relatively minor modifications to the claims and confirmed patentable over the submitted references. The reexamination of Patent 944 is currently pending. If the PTO does not confirm the claims in this patent as patentable, our patent protection with respect to FACTIVE tablets in the U.S. may be weakened.

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Under our agreement with Vicuron, we obtained an exclusive license to develop and market oral Ramoplanin in the United States and Canada. The patents that we license to Ramoplanin under our agreement with Vicuron include claims relating to methods of manufacturing Ramoplanin as well as methods increasing the yield of the active compound. We also have applications pending relating to various novel uses of Ramoplanin. The patent covering the chemical composition of Ramoplanin has expired. To provide additional protection for Ramoplanin, we rely on proprietary know-how relating to maximizing yields in the manufacture of Ramoplanin, and intend to rely on the five year data exclusivity provisions under the Hatch-Waxman Act.

Vicuron has the obligation under our agreement to prosecute patents relating to Ramoplanin that are made by Vicuron personnel or conceived jointly by our personnel and Vicuron s personnel. We have the obligation to prosecute patents relating to Ramoplanin that are made solely by our personnel. We have the right to control any suits brought by a third party alleging that the manufacture, use or sale of Ramoplanin in our licensed field in the United States or Canada infringes upon our rights. We will bear the costs of any such actions; provided that if we are obligated to pay any royalties or other payments to a third party to sell Ramoplanin as a result of this litigation, Vicuron is obligated to pay that expense. We also have the primary right to pursue actions for infringement of any patent licensed from Vicuron within the United States and Canada within our licensed field. Vicuron has the primary right to pursue actions for infringement of any patents that it licenses to us outside of our licensed field within the United States and Canada and for all purposes outside of the United States and Canada. If the party with the primary right to pursue the infringement action elects not to pursue it, the other party generally has the right to pursue it. The costs of any infringement actions are first paid out of any damages recovered and are then allocated to the parties depending upon their interest in the suit.

We have exclusively licensed rights from Vernalis for the research, development and commercialization of certain anti-infectives under Vernalis patent portfolio relating to metalloenzyme inhibitors (including peptide deformylase inhibitors), their uses and related targets.

Our own patent portfolio also comprises patents relating to DNA-nanobinder technology and their applications as anti-infective therapeutics. In addition, under our license with California Institute of Technology, we were granted rights to U.S. patents and patent applications related to DNA-nanobinder technology. Certain patents and patent applications relating to DNA-nanobinder technology resulted from research funded by the U.S. government.

We also rely upon trademarks, unpatented trade secrets and improvements, unpatented know-how and continuing technological innovation to develop and maintain our competitive position. We generally protect this information with confidentiality agreements that provide that all confidential information developed or made known to others during the course of the employment, consulting or business relationship shall be kept confidential except in specified circumstances. Agreements with employees provide that all inventions conceived by the individual while employed by us are our exclusive property. We cannot guarantee, however, that these agreements will be honored, that we will have adequate remedies for breach if they are not honored or that our trade secrets will not otherwise become known or be independently discovered by competitors.

Competition

FACTIVE tablets are approved for the treatment of community-acquired pneumonia of mild to moderate severity and acute bacterial exacerbations of chronic bronchitis. There are several classes of antibiotics that are primary competitors for the treatment of these indications, including:

- other fluoroquinolones such as Levaquin® (levofloxacin), a product of Ortho-McNeil Pharmaceutical, Inc., Tequin® (gatifloxacin), a product of Bristol-Myers Squibb Company, and Cipro® (ciprofloxacin) and Avelox® (moxifloxacin), both products of Bayer Corporation;

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- macrolides such as Biaxin® (clarithromycin), a product of Abbott Laboratories and Zithromax® (azithromycin), a product of Pfizer Inc.; and

- penicillins such as Augmentin® (amoxicillin/clavulanate potassium), a product of GlaxoSmithKline.

In addition, a new drug application for Ketek®, a ketolide antibiotic from Aventis Pharmaceuticals, has been submitted to the FDA and Ketek is currently marketed in Europe. Many generic antibiotics are also currently prescribed to treat these infections.

Ramoplanin is currently in development for the prevention of bloodstream infections caused by vancomycin-resistant enterococci (VRE). We have no knowledge of any product currently approved by the FDA for this indication, nor are we aware of any product candidate currently in clinical trials for this indication. It is possible that competition exists without our knowledge and that current discovery and preclinical efforts are ongoing for this indication. Ramoplanin is also in clinical development for the treatment of *Clostridium difficile*-associated diarrhea (CDAD). We are aware of two products currently utilized in the marketplace Vancomin® (vancomycin), a product of Eli Lilly, and metronidazole, a generic product for treatment of this indication. We are also aware of at least three companies with products in development for the treatment of CDAD a Geltex/Genzyme compound in Phase II; an ImmuCell compound in Phase I/II; and an Acambis compound in Phase I/II. It is also possible that other companies are developing competitive products for this indication.

We are also aware that Vicuron and Novartis Pharma are jointly developing PDF inhibitor agents that may compete with any PDF products we develop.

All of our other internal product programs are in early stages and are not yet indication specific. Our alliance-related product development programs are also all in preclinical stages, and it is therefore not possible to identify any product profiles or competitors for these product development programs at this time. Our industry is very competitive and it therefore is likely that if and when product candidates from our early stage internal programs or our alliance programs reach the clinical development stage or are commercialized for sale, these products will also face competition.

The biopharmaceutical industry generally, and our drug discovery and development programs specifically, are characterized by rapidly evolving technology and intense competition. Our competitors include pharmaceutical and biotechnology companies both in the United States and abroad. Many of our competitors have substantially greater capital resources, facilities and human resources than we do.

Competition with respect to our product candidates is and will be based on, among other things:

- our ability to obtain regulatory approvals for our product candidates in a cost efficient and timely manner and subsequently remain in regulatory compliance,

- our ability and our partners ability to develop and commercialize therapeutic, vaccine and diagnostic products based upon our discoveries,

- our ability to attract and retain qualified personnel,

- our ability to obtain patent protection,

our ability to develop internally or in-license product candidates for clinical development, and

our ability to secure sufficient capital resources to fund our research, clinical development and sales and marketing operations.

Because we rely primarily on in-licensing and acquisitions of products and product candidates to expand our portfolio, it is important to note that we may also face increasing competition for in-licensing and acquisition opportunities from leading pharmaceutical and biotechnology companies. We cannot be certain that we will be able to in-license product opportunities in the future or acquire new products. Competitive disadvantages in any of these areas could materially harm our business and financial condition.

Government Regulation

Regulation by governmental entities in the United States and other countries will be a significant factor in the development, manufacturing and marketing of any product candidates that we develop or commercialize. The extent to which such regulation may apply to our collaborators or us will vary depending on the nature of the product. Virtually all of our or our collaborators pharmaceutical products will require regulatory approval by governmental agencies prior to commercialization. In particular, the FDA in the United States and similar health authorities in foreign countries subject human therapeutic and vaccine products to rigorous preclinical and clinical testing and other approval procedures. Various U.S. federal and, in some cases, state statutes and regulations also govern or influence the manufacturing, safety, labeling, storage, record keeping and marketing of human therapeutic and vaccine products. Obtaining these approvals and complying with appropriate federal and foreign statutes and regulations requires a substantial amount of time and financial resources.

The FDA regulates human therapeutic products in one of three broad categories: drugs, biologics or medical devices. Our lead product, FACTIVE tablets, has already received FDA marketing approval for the treatment of community-acquired pneumonia of mild severity and acute bacterial exacerbations of chronic bronchitis. Our most advanced product candidate, Ramoplanin, currently being studied for the prevention of bloodstream infections caused by vancomycin-resistant enterococci and treatment of *Clostridium difficile*-associated diarrhea, will be regulated by the Center for Drug Evaluation and Research (CDER). Products developed as a result of our development programs could potentially fall into all three categories. The FDA generally requires the following steps for pre-market approval of a new drug or biological product:

- preclinical laboratory and animal tests,
- submission to the FDA of an investigational new drug application, or IND, which must become effective before clinical trials may begin,
- adequate and well-controlled human clinical trials to establish the safety and efficacy of the product for its intended indication,
- submission to the FDA of a marketing application; a new drug application, or NDA, if the FDA classifies the product as a new drug; or a biologics license application, or BLA, if the FDA classifies the product as biologic, and
- FDA review of the marketing application and NDA or BLA in order to determine, among other things, whether the product is safe and effective for its intended uses and is appropriately manufactured.

Our collaborators or we may also develop diagnostic products based upon the human or pathogen genes that we identify. We believe that the FDA is likely to regulate these diagnostic products as devices rather than drugs or biologics. The nature of the FDA requirements applicable to diagnostic devices depends on how the FDA classifies the diagnostic devices. The FDA most likely will classify a diagnostic device that our collaborators or we develop as a Class III device, requiring pre-market approval. Obtaining premarket approval involves the following process, rather like that of obtaining a BLA or a NDA, which may be costly and time-consuming:

- conducting pre-clinical studies,
- obtaining an investigational device exemption to conduct clinical tests,
- conducting clinical trials,

filing a pre-market approval application with safety and efficacy data and manufacturing information, and

attaining FDA approval for a specific intended use.

Products on the market are subject to continual review by the FDA. Therefore, subsequent discovery of previously unknown problems, or failure to comply with the applicable regulatory requirements may result in restricted marketing or withdrawal of the product from the market and possible civil or criminal sanctions. The FDA also may subject biologic products to batch certification and lot release requirements. There are additional regulatory requirements for products marketed outside the United States governing the conduct of clinical trials, product licensing, advertising and promotion, post-approval reports, manufacturing, pricing and reimbursement.

As a post-marketing study commitment, the FDA has required a prospective, randomized study comparing FACTIVE tablets (5,000 patients) to an active comparator (2,500 patients) in patients with CAP or ABECB. This study will include patients of different ethnicities, to gain safety information in populations not substantially represented in the existing clinical trial program, specifically as it relates to rash. Patients will be evaluated for clinical and laboratory safety. This Phase IV trial is expected to commence proximate to the product launch in the U.S. The results of this trial could restrict our ability to commercialize FACTIVE tablets.

Manufacturing facilities that produce drugs, biologics or medical devices are also subject to extensive regulation both by the FDA and foreign regulatory authorities. These regulations require, among other things, that our facilities and the facilities of third parties, such as LG Life Sciences, that produce products for us, be registered with the FDA, comply with current Good Manufacturing Practices and pass periodic inspections by the FDA. Facilities in foreign countries may be subject to inspection by FDA, local regulators or both. Current Good Manufacturing Practices, or cGMP, require extensive recordkeeping, quality control, documentation and auditing to ensure that products meet applicable specifications. Failure to comply with these requirements can result in warning letters, requirements of remedial action, and, in the case of more serious failures, suspension of manufacturing, seizure or recall of product and fines and penalties. Compliance with these requirements can be time consuming, costly and can result in delays in product approval or product sales.

Sales and Marketing

We have rights to market FACTIVE tablets in North America and parts of Europe.

Our current plan is initially to market and sell FACTIVE tablets through our own sales and marketing organization in the U.S. We are currently planning to hire sales representatives that will focus on high-prescribing primary care physicians in large markets and on infectious diseases experts. We intend to seek a co-promotion partner in the U.S. for future periods to broaden our marketing efforts. We are also building a team of professionals with experience in medical education, insurance and government reimbursement, medical affairs, marketing, advertising and scientific communications throughout this year and into 2005. It is our plan to leverage the expertise of this sales and marketing team to penetrate the fluoroquinolone market with the launch of FACTIVE tablets in summer 2004 and introduce FACTIVE tablets to the medical community.

We believe that the commercial success of FACTIVE tablets, especially in territories outside of the U.S., will benefit from the additional resources that a pharmaceutical marketing partner would provide. We anticipate that we will rely upon a co-promotion partner in our licensed territories in Europe and Canada to facilitate the filing of required regulatory submissions, to assist with necessary reimbursement discussions and to help us market and sell the product in those territories.

We have the exclusive right to market Ramoplanin in the U.S. and Canada, if approved by Canadian regulatory authorities. We plan to use the sales and marketing team we build for FACTIVE tablets to facilitate commercialization of Ramoplanin in the U.S. and Canada.

Manufacturing

Under the terms of our licensing agreement with LG Life Sciences, LG Life Sciences has agreed to supply all of our anticipated commercial requirements for FACTIVE bulk drug substance and we have agreed to purchase all of our requirements for the bulk drug substance from LG Life Sciences. LG Life Sciences is expected to supply the FACTIVE bulk drug substance from its manufacturing facility in South Korea. In addition, LG Life Sciences is obligated to provide us with finished product until the termination or expiration of

LG Life Sciences agreement with SB Pharmco Puerto Rico, Inc., or SB Pharmco. LG Life Sciences has an agreement with SB Pharmco pursuant to which SB Pharmco will supply finished FACTIVE product to LG Life Sciences. The term of this agreement ends on June 30, 2004 but, subject to the satisfaction of certain requirements, may be extended by LG Life Sciences to September 30, 2004. We are currently in discussions with new providers of finished products to assume these responsibilities for subsequent periods. We estimate that it will take 12 to 18 months to qualify a new provider of finished products. We expect to obtain quantities of FACTIVE tablets from SB Pharmco that will provide us with sufficient inventory until the new provider can be qualified. If we are unable to qualify a new provider by the time that our supply of finished product to be received from SB Pharmco is exhausted, our supply of FACTIVE product would be interrupted.

The terms of our agreement for Ramoplanin obligate the licenso