



SECURITIES AND EXCHANGE COMMISSION

WASHINGTON, D.C. 20549

**FORM 8-K**

CURRENT REPORT  
PURSUANT TO SECTION 13 OR 15(D)  
OF THE SECURITIES EXCHANGE ACT OF 1934

Date of Report: December 16, 2003

**BioCryst Pharmaceuticals, Inc.**

(Exact Name of Registrant as Specified in Charter)

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

**000-23186**  
(Commission  
File Number)

**62-1413174**  
(IRS Employer  
Identification #)

**2190 Parkway Lake Drive, Birmingham, Alabama 35244**  
(Address of Principal Executive Office)

**(205) 444-4600**  
(Registrant's telephone number, including area code)

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### **Item 5. Other Events and Regulation FD Disclosure.**

The Company is hereby filing on this Current Report on Form 8-K an updated description of the Company's business, risk factors and management's discussion and analysis of financial condition and results of operations. As a result of developments during 2003, the Company believes that certain of the information and disclosure previously reported under the requirements of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), should be updated and amended to reflect the Company's current situation.

This updated information should be read in conjunction with our Annual Report on Form 10-K for our fiscal year ended December 31, 2002 and our Quarterly Report on Form 10-Q for our fiscal quarter ended September 30, 2003. Other than as indicated above, the Company's Annual Report on Form 10-K and Quarterly Reports on Form 10-Q have not been updated to reflect developments subsequent to the periods covered by those reports.

### ***Forward-Looking Statements***

This Current Report on Form 8-K contains certain statements of a forward-looking nature relating to future events or the future financial performance of the Company. Such statements are only predictions and the actual events or results may differ materially from the results discussed in the forward-looking statements. Factors that could cause or contribute to such differences include those discussed herein as well as those discussed in other filings made by the Company with the Securities and Exchange Commission, including the Company's Annual Report on Form 10-K.

### **Item 7. Exhibits.**

<b>Exhibit No.</b>	<b>Description</b>
99.1	Updated description of the Company's business, risk factors and management's discussion and analysis of financial condition and results of operations.

**SIGNATURES**

Pursuant to the requirements of the Securities Exchange Act of 1934, the Registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

Dated: December 16, 2003

BioCryst Pharmaceuticals, Inc.

By: /s/ Charles E. Bugg

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Charles E. Bugg, Ph.D.  
Chairman and Chief Executive Officer

By: /s/ Michael A. Darwin

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Michael A. Darwin  
Chief Financial Officer and Chief  
Accounting Officer

**EXHIBIT INDEX**

<b>Item</b>	<b>Description</b>
99.1	Updated Description of Company's Business, Risk Factors and Management's Discussion and Analysis of Financial Condition and Results of Operations

## BUSINESS

### Overview

BioCryst Pharmaceuticals, Inc. is a biotechnology company focused on designing, optimizing and developing novel small molecule pharmaceuticals that block key enzymes essential for cancer, cardiovascular and autoimmune diseases and viral infections. Our most advanced drug candidate, BCX-1777, is an investigational purine nucleoside phosphorylase (PNP) inhibitor for the treatment of T-cell mediated disorders.

### Our Business Strategy

Our business strategy is to use structure-based drug design technologies to develop innovative, small-molecule pharmaceuticals to treat a variety of diseases and disorders. We focus our drug development efforts on building potent, selective inhibitors of enzymes associated with targeted diseases. Enzymes are proteins that cause or enable biological reactions necessary for the progression of the disease or disorder. The specific enzymes on which we focus are called enzyme targets. BioCryst aims to design compounds that will inhibit an enzyme target by fitting the active site of a particular enzyme. Inhibition means interfering with the functioning of an enzyme target, thereby stopping or slowing the progression of the disease or disorder. The principal elements of our strategy are:

- **Select and License Promising Enzyme Targets for the Development of Small-Molecule Pharmaceuticals.** We use our technical expertise and network of academic and industry contacts to evaluate and select promising enzyme targets to license for the development of small-molecule pharmaceuticals. We choose enzyme targets that meet as many of the following criteria as possible:
  - serve important functions in disease pathways;
  - have known animal or cell-based models that would be indicative of results in humans;
  - address large potential markets and significant unmet medical needs, including pursuing niche markets where the results have potential application to broader markets and needs;
  - have multiple potential clinical applications; and
  - offer rapid development and commercialization opportunities.
- **Focus on High Value-Added Structure-Based Drug Design Technologies.** We focus our drug discovery activities and expenditures on applications of structure-based drug design technologies to design and develop drug candidates. Structure-based drug design is a process by which we design a drug candidate through detailed analysis of the enzyme

target, which the drug candidate must inhibit in order to stop the progression of the disease or disorder. We believe that structure-based drug design is a powerful tool for efficient development of small-molecule drug candidates that have the potential to be safe, effective and relatively inexpensive to manufacture. Our structure-based drug design technologies typically allow us to design and synthesize multiple drug candidates that inhibit the same enzyme target. We believe this strategy can lead to broad patent protection and enhance the competitive advantages of our compounds.

- ***Develop or License Inhibitors that are Promising Candidates for Commercialization.*** We test multiple compounds to identify those that are most promising for clinical development. We base our selection of promising development candidates on desirable product characteristics, such as initial indications of safety and efficacy. We believe that this focused strategy allows us to eliminate unpromising candidates from consideration sooner without incurring substantial clinical costs. In addition, we select drug candidates on the basis of their potential for relatively efficient Phase I and Phase II clinical trials that require fewer patients to initially indicate safety and efficacy. We will consider, however, more complex candidates with longer development cycles if we believe that they offer promising commercial opportunities.

An important element of our business strategy is to control fixed costs and overhead through contracting and entering into license agreements with other parties. We maintain a streamlined corporate infrastructure that focuses on our strongest areas of expertise. By contracting with other specialty organizations, we believe that we can control costs, enable our drug candidates to reach the market more quickly and reduce our business risk. Key elements of our contracting strategy include:

- ***Entering Into Relationships with Academic Institutions and Biotechnology Companies.*** Many academic institutions and biotechnology companies perform extensive research on the molecular and structural biology of potential drug development targets. By entering into relationships with these institutions, we believe we can significantly reduce the time, cost and risks involved in drug development. Our collaborative relationships with such organizations may lead to the licensing of one or more drug targets or compounds. Upon licensing a drug target or promising compound from one of these institutions, the scientists from the institution typically become working partners as members of our structure-based drug design teams. We believe this makes us a more attractive development partner to these scientists. In addition, we collaborate with outside experts in a number of areas, including crystallography, molecular modeling, combinatorial chemistry, biology, pharmacology, oncology, cardiology, immunology and infectious diseases. These collaborations enable us to complement our internal capabilities without adding costly overhead. We believe this strategy allows us to save valuable time and expense, and further diversify and strengthen our portfolio of drug candidates. An example of such a collaborative relationship is the arrangement that we have with The University of Alabama at Birmingham, or UAB, which has resulted in the initiation of several of our early drug development programs.
- ***Developing Drug Development Candidates or Licensing Them to Other Parties.*** We generally plan to advance drug candidates through initial and/or early-stage drug



development. For larger disease indications requiring complex clinical trials, our strategy is to license drug candidates to pharmaceutical or biotechnology partners for final development and global marketing. We believe partnerships are a good source of development payments, license fees, milestone payments and royalties. They also reduce the costs and risks, and increase the effectiveness, of late-stage product development, regulatory approval, manufacturing and marketing. We believe that focusing on discovery and early-stage drug development while benefiting from our partners' proven development and commercialization expertise will reduce our internal expenses and allow us to have a larger number of drug candidates progress to late-stage drug development. However, after establishing a lead product candidate, we are willing to license that candidate during any stage of the development process we determine to be beneficial to the company and to the ultimate development and commercialization of that drug candidate. For some smaller niche disease indications markets, we may choose to complete development, manufacture, and where appropriate market and distribute any approved drugs ourselves, such as BCX-1777 for T-cell leukemias.

## Products in Development

The following table summarizes BioCryst's development projects as of November 30, 2003:

Program and Candidate Disease Category/Indication	Delivery Form	Development Stage	Worldwide Rights
<b>PNP Inhibitor (BCX-1777)</b> Oncology, T-cell related diseases	Intravenous	Phase I	BioCryst
	Oral	Phase I	BioCryst
<b>Tissue Factor/Factor VIIa Inhibitors</b> Cardiovascular/Acute coronary events, anticoagulation, oncology	Intravenous (BCX-3607)	Preclinical	BioCryst
	Oral	Lead Optimization	BioCryst
<b>Hepatitis C Polymerase Inhibitors</b> Viral/Hepatitis C	Oral	Lead Optimization	BioCryst
<b>PNP Inhibitor (BCX-4208)</b> Autoimmune, inflammation/ T-cell related diseases, Psoriasis	Oral	Preclinical	BioCryst

### *T-cell Related Diseases*

*Overview.* The link between T-cell proliferation and the purine nucleoside phosphorylase, or PNP, enzyme was first discovered approximately twenty-five years ago when a patient, who was genetically deficient in PNP, exhibited limited T-cell activity, but reasonably normal activity of other immune functions. In other patients lacking PNP activity, the T-cell population was

selectively depleted; however, B-cell function tended to be normal. Based on these findings and the results of cell culture studies, inhibiting PNP produces selective suppression of T-cells without significantly impairing the function of other cells.

The human immune system employs specialized cells, including T-cells, to control infection by recognizing and attacking disease-causing viruses, bacteria and parasites. T-cells are an essential part of the body's immune system that serve a dual purpose to both orchestrate and participate in the body's immune response. For the most part, this system works flawlessly to protect the body. However, when T-cells multiply uncontrollably, T-cell proliferative diseases, including T-cell cancers, occur.

*Acute Lymphoblastic Leukemia.* The most common form of leukemia in children is acute lymphoblastic leukemia (also known as ALL). According to the American Cancer Society, 3,600 new cases (adult and children combined) will be diagnosed in the United States in 2003. ALL results from an acquired injury to the DNA of a single cell in the bone marrow.

*T-cell Lymphoma.* Lymphoma is a general term for a group of cancers that originate in the lymphatic system. About 53,000 Americans will be diagnosed with a non-Hodgkin's lymphoma in 2003 and approximately 15% of these will be considered T-cell lymphomas. T-cell lymphoma results when a T-lymphocyte (a type of white blood cell) undergoes a malignant change and begins to multiply, eventually crowding out healthy cells and creating tumors, which enlarge the lymph nodes and invade other sites in the body. Cutaneous T-cell lymphoma (CTCL) is a primary skin neoplasm and accounts for nearly 50% of all T-cell malignancies.

*T-cell Mediated Autoimmune Diseases.* Diseases such as psoriasis, rheumatoid arthritis, multiple sclerosis, and Crohn's appear to have activated T-cells as a major part of their pathogenesis. Therefore, inhibition and/or elimination of such cells could have a profound and beneficial effect on these diseases.

*PNP Inhibition.* PNP is an enzyme that plays an important role in T-cell proliferation, because it is necessary to maintain normal DNA synthesis in T-cells. Selective inhibition of PNP has an accumulation effect on certain nucleosides, including deoxyguanosine. As the concentration of deoxyguanosine increases within T-cells, it is converted by specific enzymes to deoxyguanosine triphosphate. A high concentration of deoxyguanosine triphosphate in T-cells blocks DNA synthesis and thus inhibits cell division.

#### ***Our PNP Inhibitor(s)***

*Background.* In June 2000, we licensed a series of potent inhibitors of purine nucleoside phosphorylase from Albert Einstein College of Medicine of Yeshiva University (AECOM) and Industrial Research, Ltd, New Zealand (IRL). The lead drug candidate from this collaboration, BCX-1777, is a more potent inhibitor of human lymphocyte proliferation than other previously known PNP inhibitors. Extensive preclinical studies and early patient data indicate that BCX-1777 can modulate T-cell activities. BCX-1777 is an investigational PNP inhibitor for the potential treatment of T-cell leukemias and lymphomas.

During 2002, we exercised the option to add a new compound, BCX-4208, to the series of inhibitors of PNP licensed from AECOM and IRL. Preclinical results indicate that BCX-4208

is a more potent inhibitor than BCX-1777. We plan to develop BCX-4208 for autoimmune diseases such as psoriasis and rheumatoid arthritis.

### ***Current Development Strategy***

*Overview.* The first clinical trial with an intravenous formulation of BCX-1777 is a Phase I clinical trial for patients with relapsed or refractory T-cell acute lymphoblastic leukemia (ALL) and T-cell lymphoma. The Phase I trial is an open-label dose-escalation study of BCX-1777 in relapsed or refractory aggressive T-cell malignancies, which are among the most difficult cancers to treat by current therapies. Because of the clinical results seen to this point and a recent discovery by our colleagues at the M.D. Anderson Cancer Center, we started three additional trials in 2003 for refractory patients with other types of hematologic malignancies, cutaneous T-cell lymphoma, and solid tumors. Preclinical studies at the M.D. Anderson Cancer Center indicate that BCX-1777 induces the same biochemical changes in various other types of leukemia cells that are responsible for the inhibition of T-leukemia cells, which suggest that BCX-1777 may be even more broadly applicable than originally expected.

*BCX-1777 Clinical Development for Aggressive T-cell Malignancies.* The Phase I clinical trial was developed in close collaboration with experts at The University of Texas M. D. Anderson Cancer Center. Despite encouraging results observed with other T-cell specific agents, the prognosis for patients with relapsed or refractory leukemia or lymphoma is poor and treatment options remain limited. The goal of the Phase I clinical trial is to determine the safety, biochemical and metabolic profile and therapeutic effect produced by BCX-1777 as it relates to the proposed mechanism of action in the inhibition of proliferating T-lymphocytes in patients with T-cell ALL or T-cell lymphoma. Our strategy for future development of BCX-1777 is to pursue with the FDA both orphan drug and fast-track designations. We are also designing a Phase II trial for intravenous BCX-1777, which, assuming successful completion of the current trials, we plan to begin in early 2004 to treat patients with T-cell leukemias. We also plan to initiate a second Phase II trial in early 2004 with intravenous BCX-1777 for treatment of patients with cutaneous T-cell lymphoma (CTCL). Our current intent is for BioCryst itself to market and distribute BCX-1777 in the United States for treatment of T-cell cancers

Early Phase I studies with oral BCX-1777 are currently in progress at the Cleveland Clinic, and we plan to initiate a Phase I/II CTCL clinical trial with oral BCX-1777 during the first half of 2004.

### **Tissue Factor/Factor VIIa (BCX-3607)**

#### ***Overview***

A series of complicated reactions take place in the body whenever a blood clot begins to form. The major initiator of these reactions is an enzyme system called the Tissue Factor/Factor VIIa (TF/FVIIa) complex. Animal tests show that various inhibitors of the TF/FVIIa complex can minimize blood clot formation as well as inflammatory responses. This sort of inhibition has been tested with a number of biological agents including the natural inhibitor of the pathway, synthetic peptides and protein inhibitors, and antibodies against tissue factor. However, there are no small molecule drugs currently on the market that intervene at the TF/FVIIa level.

We believe that small molecule inhibitors of TF/FVIIa may potentially be useful for treating acute coronary syndromes and complications associated with cardiovascular procedures, such as coronary angioplasty and stent insertions, because any type of damage to arteries and blood vessels exposes tissue factor, which then triggers clot formation. Myocardial infarction, unstable angina, and restenosis during and following angioplasty procedures are all potential treatment targets. In addition, tissue factor is involved in angiogenesis, or new blood vessel growth, and inhibitors of the TF/FVIIa complex are believed to have potential as anti-angiogenesis agents for use in oncology.

*Background.* We have an agreement with Sunol Molecular Corp. to expedite the discovery of new drug candidates designed to inhibit TF/FVIIa. Under the terms of this agreement, Sunol supplies us protein for our drug design program.

#### ***Current Development Strategy***

Our intravenous TF/FVIIa inhibitor project has emerged as our second most advanced development program. We have designed and synthesized a group of compounds that are potent and selective inhibitors of TF/FVIIa and further optimization is ongoing. Currently we have identified one compound (BCX-3607) for clinical development. The goal is to advance BCX-3607 into Phase I clinical development for treatment of unstable angina during early 2004, while seeking a partner to develop and potentially commercialize this class of inhibitors. We also plan to use the Phase I data to support a Phase I/II trial later in 2004 for use of BCX-3607 in oncology as an inhibitor of angiogenesis.

We are also currently working to identify a compound for preclinical development of a TF/FVIIa inhibitor in oral form.

### **Hepatitis C**

#### ***Overview***

Hepatitis C virus (HCV) infection has been described in the New England Journal of Medicine as the nation's most common chronic blood-borne infection. Up to 3% of the world population has been infected with HCV. According to the National Centers for Disease Control, as many as 75-85% of those infected with HCV will have chronic infection and 70% of those will develop chronic liver disease. While there are several approved treatments for chronic HCV using a combination therapy of interferon and ribavirin, there are some potentially severe side effects to these treatments.

*Background.* In June 2000, we licensed intellectual property from Emory University related to the Hepatitis C polymerase target associated with Hepatitis C viral infections. Under the terms of the agreement, the research investigators from Emory provide us with materials and technical insight into the target.

#### ***Current Development Strategy***

We are targeting HCV polymerase through collaborative and in-house efforts. Specifically, we are focused on development of orally active inhibitors against the RNA-

dependent RNA polymerase. Competition for this target is less intense than for the HCV protease target and history suggests the likelihood of designing a useful inhibitor against this target may be better than for the more difficult protease.

Currently, we are designing, synthesizing and screening potential compounds against HCV polymerase. Specifically, our scientists are measuring the potency and ability of potential drug candidates to block the replication of HCV polymerase in vitro, or in test tubes. These experiments measure the potency of each selected compound's ability to block replication. Advanced screening is also underway to measure the fit of promising compounds in the HCV polymerase active site using X-ray crystallography and computer molecular modeling. The goal is to identify a series of compounds that are potent in vitro inhibitors of the active site of the HCV polymerase for further testing and lead optimization.

We also have agreements in place with the National Institute of Allergy and Infectious Diseases, a unit of The National Institutes of Health, and the U.S. Army Medical Research Institute of Infectious Diseases to assay promising inhibitors from the HCV polymerase program for activity against Severe Acute Respiratory Syndrome (SARS), West Nile and Ebola viruses.

## **PNP Inhibitor (BCX-4208)**

### *Overview*

We believe that the results to date of our Phase I trials of BCX-1777 support the principle that inhibition of PNP has a direct effect on proliferation of activated T-lymphocytes. We are now developing BCX-4208, a second-generation PNP inhibitor, as a drug candidate for the treatment of T-cell mediated autoimmune diseases, including psoriasis. Although BCX-4208 and BCX-1777 are both investigational PNP inhibitors, BCX-4208 differs from BCX-1777 in significant ways. For example, BCX-4208 is more potent, with the ability to modulate T-cell activity for longer period of time. Thus, BCX-4208 has potential advantages over BCX-1777 for the treatment of diseases requiring long-term, chronic administration of a PNP inhibitor.

### *Current Development Strategy*

During 2003, we have conducted a series of preclinical studies of BCX-4208. We are preparing to begin preclinical toxicology studies, and our goal is to advance BCX-4208 into Phase I clinical development for treatment of patients with psoriasis in the second half of 2004.

### **Structure-Based Drug Design**

Structure-based drug design is a drug discovery approach by which we design synthetic compounds from detailed structural knowledge of the active sites of enzyme targets associated with particular diseases. Enzymes are proteins that act as catalysts for many vital biological reactions. Our goal generally is to design a compound that will fit in the active site of an enzyme (the active site of an enzyme is the area into which a chemical or biological molecule fits to initiate a biochemical reaction) and thereby interfere with the progression of disease.

Our structure-based drug design involves the application of both traditional biology and medicinal chemistry and an array of advanced technologies. We use X-ray crystallography,

computer modeling of molecular structures and advanced chemistry techniques to focus on the three-dimensional molecular structure and active site characteristics of the enzymes that control cellular biology.

We believe that structure-based drug design technologies are superior to drug screening techniques. By identifying the target enzyme in advance and by discovering the chemical and molecular structure of the enzyme, we believe it is possible to design a better drug to interact with the enzyme. In addition, the structural data obtained by X-ray crystallographic analysis allow additional analysis and compound modification at each stage of the biological evaluation. This capability makes structure-based drug design a powerful tool for efficient development of drugs that are highly specific for particular enzyme target sites.

## **Research and Development**

We initiated our research and development program in 1986, with drug synthesis beginning in 1987. We have assembled a scientific research staff with expertise in a broad base of advanced research technologies including protein biochemistry, X-ray crystallography, chemistry and pharmacology. Our research facilities include protein biochemistry and organic synthesis laboratories, testing facilities, X-ray crystallography, computer and graphics equipment and facilities to make drug candidates on a small scale.

During the years ended December 31, 2000, 2001 and 2002, we spent an aggregate of \$38.1 million on research and development. Approximately \$25.8 million of that amount was spent on in-house research and development, and \$12.3 million was spent on contract research and development.

## **Collaborative Relationships**

### *Corporate Alliances*

*Sunol Molecular Corp.* In April 1999, we entered into an agreement with Sunol. This agreement requires Sunol to conduct research and supply us with protein targets for drug design to expedite the discovery of new drug candidates designed to inhibit Tissue Factor/Factor VIIa for our cardiovascular program.

### *Academic Alliances*

*The University of Alabama at Birmingham.* We have had a close relationship with The University of Alabama at Birmingham (UAB), since our formation. Our Chairman and Chief Executive Officer, Dr. Charles E. Bugg, was the previous Director of the UAB Center for Macromolecular Crystallography, and our President, Chief Operating Officer and Medical Director, Dr. J. Claude Bennett, was the former President of UAB, the former Chairman of the Department of Medicine at UAB and a former Chairman of the Department of Microbiology at UAB. Several of our consultants are employed by UAB. UAB has a large X-ray crystallography center with approximately 110 full-time staff members and approximately \$15 million in research grants and contract funding in 2003. Several of our early programs originated at UAB.

We currently have agreements with UAB for influenza neuraminidase and complement inhibitors. Under the terms of these agreements, UAB performed specific research for us in return for research payments and license fees. UAB has granted us certain rights to any discoveries in these areas resulting from research developed by UAB or jointly developed with us. We have agreed to pay royalties on sales of any resulting product and to share in future payments received from other third-party collaborators. UAB received a portion of license fees and milestone payments we received from RWJPRI and Ortho-McNeil for our former influenza collaboration. UAB would receive a portion of any future license fees, milestone payments and royalties if we were to obtain another partner for our influenza program. We have completed the research under the UAB influenza agreement. We funded the research program under the complement inhibitors agreement through March 2002, which entitled us to an assignment of, or a right to an exclusive license for, any inhibitors of specified complement enzymes developed by UAB scientists during the period of support or for a one-year period thereafter. These two agreements have initial 25-year terms, are automatically renewable for five-year terms throughout the life of the last patent and are terminable by us upon three-month's notice and by UAB under certain circumstances.

*Albert Einstein College of Medicine of Yeshiva University and Industrial Research, Ltd, New Zealand.* In June 2000, we licensed a series of potent inhibitors of purine nucleoside phosphorylase, or PNP, from Albert Einstein College of Medicine of Yeshiva University and Industrial Research, Ltd., New Zealand. The lead drug candidate from this collaboration is BCX-1777. We have the rights to develop and ultimately distribute this, or any other, drug candidate that might arise from research on these inhibitors. For example, in 2003 we obtained the rights to another compound from this series, BCX-4208, which is currently in preclinical development. We have agreed to pay certain milestone payments for future development of these inhibitors, pay certain royalties on sales of any resulting product, and to share in future payments received from other third-party collaborators, if any. We can terminate this agreement at any time by giving 60 days advance notice.

*Emory University.* In June 2000, we licensed intellectual property from Emory University related to the Hepatitis C polymerase target associated with Hepatitis C viral infections. Under the terms of the agreement, the research investigators from Emory provide us with materials and technical insight into the target. We have agreed to pay Emory royalties on sales of any resulting product and to share in future payments received from other third party collaborators, if any. We can terminate this agreement at any time by giving 90 days advance notice.

### **Patents and Proprietary Information**

Our success will depend in part on our ability to obtain and enforce patent protection for our products, methods, processes and other proprietary technologies, preserve our trade secrets, and operate without infringing on the proprietary rights of other parties, both in the United States and in other countries. We own or have rights to certain proprietary information, proprietary technology, issued and allowed patents and patent applications which relate to compounds we are developing. We actively seek, when appropriate, protection for our products, proprietary technology and proprietary information by means of U.S. and foreign patents, trademarks and contractual arrangements. In addition, we rely upon trade secrets and contractual arrangements to protect certain of our proprietary information, proprietary technology and products.

As of November 30, 2003, we have been issued 18 U.S. patents that expire between 2009 and 2020 and that relate to our PNP and neuraminidase inhibitor compounds. We have licensed four additional patents and two pending patents from Albert Einstein College of Medicine of Yeshiva University and one patent from Emory University. We have also filed patent applications for new processes to prepare certain PNP inhibitors. Additionally, we have 17 U.S. patent applications pending related to PNP, neuraminidase, RNA viral polymerase, paramyxovirus neuraminidase, and serine protease inhibitors. Our pending applications may not result in issued patents, and our patents may not provide us with sufficient protection against competitive products or otherwise be commercially available.

Our success is also dependent upon the skills, knowledge and experience of our scientific and technical personnel, none of which is patentable. To help protect our rights, we require all employees, consultants, advisors and collaborators to enter into confidentiality agreements which prohibit the disclosure of confidential information to anyone outside of our company and requires disclosure and assignment to us of their ideas, developments, discoveries and inventions. These agreements may not provide adequate protection for our trade secrets, know-how or other proprietary information in the event of any unauthorized use or disclosure or the lawful development by others of such information.

### **Marketing and Sales**

We currently plan to market, distribute and sell BCX-1777 in the U.S. for use in treatment of T-cell cancers. Although our general strategy is to rely on major marketing companies for worldwide commercialization of most products we may develop, we believe that we can manage the highly specialized oncology market for BCX-1777 within the U.S. Most patients with advanced T-cell malignancies in the U.S. are treated at major referral cancer centers, and we expect that many of these centers will be participating in our Phase II trials and will thus be familiar with BCX-1777 if it reaches the market. However, we lack experience in marketing, distributing and selling pharmaceutical products. Our general strategy is to rely on collaborators, licensees or arrangements with others to provide for the marketing, distribution and sales of products we may develop. We may not be able to establish and maintain acceptable commercial arrangements with collaborators, licensees or others to perform such activities. For example, In September 1998, BioCryst entered a worldwide license agreement with The R.W. Johnson Pharmaceutical Research Institute (RWJPRI) and Ortho-McNeil Pharmaceutical Inc. (Ortho-McNeil), both Johnson & Johnson companies, for development and commercialization of our influenza neuraminidase inhibitors, including peramivir.

On April 30, 2001, BioCryst announced that Ortho-McNeil and RWJPRI, gave four months prior notice of termination of the worldwide license agreement with BioCryst to develop and market products to treat and prevent viral influenza. Subsequently, all rights to peramivir returned to BioCryst.

### **Competition**

The pharmaceutical and biotechnology industries are intensely competitive. Many companies, including biotechnology, chemical and pharmaceutical companies, are actively engaged in activities similar to ours, including research and development of drugs for the



treatment of infectious, inflammatory and cardiovascular diseases and disorders. Many of these companies have substantially greater financial and other resources, larger research and development staffs, and more extensive marketing and manufacturing organizations than we do. In addition, some of them have considerable experience in preclinical testing, clinical trials and other regulatory approval procedures. There are also academic institutions, governmental agencies and other research organizations that are conducting research in areas in which we are working. They may also market commercial products, either on their own or through collaborative efforts.

We expect to encounter significant competition for any of the pharmaceutical products we plan to develop. Companies that complete clinical trials, obtain required regulatory approvals and commence commercial sales of their products before their competitors may achieve a significant competitive advantage. In addition, several pharmaceutical and biotechnology firms, including major pharmaceutical companies and specialized structure-based drug design companies, have announced efforts in the field of structure-based drug design and in the fields of PNP, Hepatitis C, and Tissue Factor/Factor VIIa.

In order to compete successfully, we must develop proprietary positions in patented drugs for therapeutic markets that have not been satisfactorily addressed by conventional research strategies and, in the process, expand our expertise in structure-based drug design. Our products, even if successfully tested and developed, may not be adopted by physicians over other products and may not offer economically feasible alternatives to other therapies.

## **Government Regulation**

The FDA regulates the pharmaceutical and biotechnology industries in the United States, and our drug candidates are subject to extensive and rigorous domestic government regulations prior to commercialization. The FDA regulates, among other things, the development, testing, manufacture, safety, efficacy, record-keeping, labeling, storage, approval, advertising, promotion, sale and distribution of pharmaceutical products. In foreign countries, our products are also subject to extensive regulation by foreign governments. These government regulations will be a significant factor in the production and marketing of any pharmaceutical products that we develop. Failure to comply with applicable FDA and other regulatory requirements at any stage during the regulatory process may subject us to sanctions, including:

- delays;
- warning letters;
- fines;
- product recalls or seizures;
- injunctions;
- penalties;

- refusal of the FDA to review pending market approval applications or supplements to approval applications;
- total or partial suspension of production;
- civil penalties;
- withdrawals of previously approved marketing applications; and
- criminal prosecutions.

The regulatory review and approval process is lengthy, expensive and uncertain. Before obtaining regulatory approvals for the commercial sale of any products, we or our licensees must demonstrate that our product candidates are safe and effective for use in humans. The approval process takes many years, substantial expenses may be incurred and significant time may be devoted to clinical development.

Before testing potential candidates in humans, we carry out laboratory and animal studies to determine safety and biological activity. After completing preclinical trials, we must file an investigational new drug application, including a proposal to begin clinical trials, with the FDA. We have filed nine investigational new drug applications to date and plan to file, or rely on future partners to file, additional investigational new drug applications in the future as our potential drug candidates advance to that stage of development. Thirty days after filing an investigational new drug application, a Phase I human clinical trial can start unless the FDA places a hold on the study.

Our Phase I trials are designed to determine safety in a small group of patients or healthy volunteers. We also assess tolerances and the metabolic and pharmacologic actions of our drug candidates at different doses. After we complete the initial trials, we conduct Phase II trials to assess safety and efficacy and establish the optimal dose in patients. If Phase II trials are successful, we or our licensees conduct Phase III trials to verify the results in a larger patient population. Phase III trials are required for FDA approval to market a drug. A Phase III trial may require hundreds or even thousands of patients and is the most expensive to conduct. The goal in Phase III is to collect enough safety and efficacy data to obtain FDA approval for treatment of a particular disease. For some clinical indications that are especially serious and for which there are no effective treatments, such as refractory cancers, conditional approval can be obtained following Phase II trials.

Initiation and completion of the clinical trial phases are dependent on several factors including things that are beyond our control. For example, the clinical trials are dependent on patient enrollment, but the rate at which patients enroll in the study depends on:

- the size of the patient population we intend to treat;
- the availability of patients;
- the willingness of patients to participate; and

- the patient meeting the eligibility criteria.

Delays in planned patient enrollment may result in increased expense and longer development timelines.

After completion of the clinical trials of a product, we or our licensees must submit a new drug application to the FDA for marketing approval before commercialization of the product. The FDA may not grant approval on a timely basis, if at all. The FDA, as a result of the Food and Drug Administration Modernization Act of 1997, has six months to review and act upon license applications for priority therapeutics that are for life-threatening or unmet medical needs. Standard reviews can take between one and two years, and can even take longer if significant questions arise during the review process. The FDA may withdraw any required approvals, once obtained.

In addition to clinical development regulations, we and our contract manufacturers and collaborators must comply with the applicable FDA current good manufacturing practice (“GMP”) regulations. GMP regulations include requirements relating to quality control and quality assurance as well as the corresponding maintenance of records and documentation. Manufacturing facilities are subject to inspection by the FDA. Such facilities must be approved before we can use them in commercial manufacturing of our potential products. We or our contract manufacturers may not be able to comply with the applicable GMP requirements and other FDA regulatory requirements. If we or our contract manufacturers fail to comply, our business, financial condition and results of operations will be materially adversely affected.

### **Human Resources**

As of November 30, 2003, we had 45 employees, of whom 34 were engaged in research and development and 11 were in general and administrative functions. Our scientific staff, 20 of whom hold Ph.D. or M.D. degrees, has diversified experience in biochemistry, pharmacology, X-ray crystallography, synthetic organic chemistry, computational chemistry, and medicinal chemistry. We consider our relations with our employees to be satisfactory.

### **Scientific Advisory Board and Consultants**

Our scientific advisory board is comprised of five scientific advisors who are leaders in certain of our core disciplines or who otherwise have specific expertise in our therapeutic focus areas. We also have consulting agreements with a number of other scientists with expertise in our core disciplines or who are specialists in diseases or treatments on which we focus. The scientific advisory board meets as a group at scheduled meetings and the consultants meet more frequently, on an individual basis, with our scientific personnel and management to discuss our ongoing research and drug discovery and development projects. The scientific advisory board consists of the following individuals:

<b>Name</b>	<b>Position</b>
Albert F. LoBuglio, M.D. (Chairman)	Professor of Medicine and the Director of The University of Alabama at Birmingham Comprehensive Cancer Center.

Name	Position
Gordon N. Gill, M.D.	Professor of Medicine and Chair of the Faculty of Basic Biomedical Sciences at the University of California, San Diego School of Medicine.
Lorraine J. Gudas, Ph.D.	Professor and Chairman of the Department of Pharmacology of Cornell Medical College and the Revlon Pharmaceutical Professor of Pharmacology and Toxicology.
Herbert A. Hauptman, Ph.D.	President of the Hauptman-Woodward Medical Research Institute, Inc. (formerly the Medical Foundation (Buffalo), Inc.), and Research Professor in Biophysical Sciences at the State University of New York (Buffalo). Recipient of the Nobel Prize in Chemistry (1985).
Hamilton O. Smith, M.D.	Professor, Molecular Biology and Genetics Department at The Johns Hopkins University School of Medicine, retired, and Scientific Director of The Institute for Bioenergy Alternatives. Recipient of the Nobel Prize in Medicine (1978).

The scientific advisors and the consultants are reimbursed for their expenses and receive nominal cash compensation in connection with their service and have been issued options and/or shares of common stock. The scientific advisors and the consultants are all employed by or have consulting agreements with entities other than us, some of which may compete with us in the future. The scientific advisors and the consultants are expected to devote only a small portion of their time to our business, although no specific time commitment has been established. They are not expected to participate actively in our affairs or in the development of our technology. Several of the institutions with which the scientific advisors and the consultants are affiliated may adopt new regulations or policies that limit the ability of the scientific advisors and the consultants to consult with us. The loss of the services of the scientific advisors and the consultants could adversely affect us to the extent that we are pursuing research or development in areas relevant to the scientific advisors' and consultants' expertise. To the extent members of our scientific advisory board or the consultants have consulting arrangements with or become employed by any of our competitors, we could be materially adversely affected.

Any inventions or processes independently discovered by the scientific advisors or the consultants may not become our property and will probably remain the property of such persons or of such persons' employers. In addition, the institutions with which the scientific advisors and the consultants are affiliated may make available the research services of their personnel, including the scientific advisors and the consultants, to our competitors pursuant to sponsored research agreements. We require the scientific advisors and the consultants to enter into confidentiality agreements which prohibit the disclosure of confidential information to anyone outside of our company and require disclosure and assignment to us of their ideas, developments, discoveries or inventions. However, our competitors may gain access to trade secrets and other proprietary information developed by us and disclosed to the scientific advisors and the consultants.

## MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS

*This discussion contains certain statements of a forward-looking nature relating to future events or the future financial performance of the Company. Such statements are only predictions and the actual events or results may differ materially from the results discussed in the forward-looking statements. Factors that could cause or contribute to such differences include those discussed below as well as those discussed in other filings made by the Company with the Securities and Exchange Commission, including the Company's Annual Report on Form 10-K.*

### Overview

Since our inception in 1986, we have been engaged in research and development activities and organizational efforts, including:

- identification and licensing of enzyme targets;
- drug discovery;
- structure-based design of drug candidates;
- small-scale synthesis of compounds;
- conducting preclinical studies and clinical trials;
- recruiting our scientific and management personnel;
- establishing laboratory facilities; and
- raising capital.

Our revenues have generally been limited to license fees, milestone payments, interest income, and collaboration research and development fees. The Company recognizes revenue in accordance with SEC Staff Accounting Bulletin No. 101, Revenue Recognition in Financial Statements ("SAB 101"). Research and development revenue on cost-reimbursement agreements is recognized as expenses are incurred, up to contractual limits. Research and development fees, license fees and milestone payments are recognized as revenue when the earnings process is complete, the Company has no further continuing performance obligations and has completed its performance under the terms of the agreement, in accordance with SAB 101. License fees and milestone payments received under licensing agreements that are related to future performance are deferred and taken into income as earned over the estimated drug development period. The Company has not received any revenues or royalties from the sale of licensed pharmaceutical products. It could be several years, if ever, before we will recognize significant revenue from royalties received pursuant to our license agreements or revenue directly from product sales. Future revenues, if any, are likely to fluctuate substantially from quarter to quarter.

We have incurred operating losses since our inception. Our accumulated deficit at September 30, 2003 was \$101.4 million. We will require substantial expenditures relating to the development of our current and future drug candidates. During the three years ended December 31, 2002, we spent 32.3% of our research and development expenses on contract research and development, including:

- payments to consultants;
- funding of research at academic institutions;
- large scale synthesis of compounds;
- preclinical studies;
- engaging investigators to conduct clinical trials;
- hiring contract research organizations to monitor and gather data on clinical trials; and
- using statisticians to evaluate the results of clinical trials.

The above expenditures for contract research and development for our current and future drug candidates will vary from quarter to quarter depending on the status of our research and development projects. For example, on June 25, 2002, we announced preliminary Phase III clinical trial data for peramivir, our investigational oral influenza neuraminidase inhibitor. The trial indicated no statistically significant difference in the primary efficacy endpoint between groups treated with peramivir and groups treated with placebo. Based on these data, we discontinued the development of peramivir. During the first nine months of 2002, our cash expenses related to this trial were approximately \$4 million. After terminating the development of peramivir, the Company streamlined its operations, reducing its workforce from 75 employees to 45 employees in order to conserve its resources and provide a longer timeframe in which to advance its other programs.

Changes in our existing and future research and development and collaborative relationships will also impact the status of our research and development projects. Although we may, in some cases, be able to control the timing of development expenses, in part by accelerating or decelerating certain of these costs, many of these costs will be incurred irrespective of whether we are able to discover drug candidates or obtain collaborative partners for commercialization. As a result, we believe that quarter-to-quarter comparisons of our financial results are not necessarily meaningful and should not be relied upon as an indication of future performance. If we fail to meet the research, clinical and financial expectations of securities analysts and investors, it could have a material adverse effect on the price of our common stock.

### **Results of Operations (three months ended September 30, 2003 compared to the three months ended September 30, 2002)**

Interest and other income decreased 46.1% to \$222,000 in the third quarter of 2003 compared to \$412,000 in the third quarter of 2002. This decrease was due to a reduction in cash and a lower interest rate environment in 2003.

Research and development expenses decreased 2.1% to \$3,105,000 in the three months ended September 30, 2003 from \$3,172,000 in the three months ended September 30, 2002. The decrease is primarily attributed to lower personnel costs due to a smaller staff in 2003, which was partially offset by an increase in the clinical development costs associated with our lead drug candidate, BCX-1777.

General and administrative expenses for the three months ended September 30, 2003 decreased 19.7% to \$526,000 as compared to \$655,000 for the same period in 2002. This decrease is primarily related to our reduced staff in 2003.

### **Results of Operations (nine months ended September 30, 2003 compared to the nine months ended September 30, 2002)**

Revenues for the nine months ended September 30, 2003 were \$796,000, compared to \$1,412,000 for the nine months ended September 30, 2002. The net loss for the nine months ended September 30, 2003 was \$9,450,000, or \$0.53 per share, compared to a net loss of \$14,193,000 or \$0.80 per share, for the same period last year. The decrease in revenues in the first nine months of 2003 was due to lower interest income as a result of the reduction in cash and a lower interest rate environment in 2003.

Research and development expenses decreased 33.8% to \$8,559,000 in the nine months ended September 30, 2003 from \$12,935,000 in the nine months ended September 30, 2002. The decrease is primarily attributable to reduced clinical trial expenses in 2003 due to the discontinuation in June 2002 of the Phase III development of peramivir. In addition, personnel and other operating costs were lower due to a smaller staff in 2003.

General and administrative expenses for the nine months ended September 30, 2003 decreased 26.5% to \$1,687,000 as compared to \$2,296,000 for the same period in 2002. This decrease is also primarily related to our reduced staff in 2003 and lower professional fees as compared to 2002 when we implemented a stockholder rights plan. The lower expenses for 2003 also reflect the fact that we had no impairment charges, compared to an impairment of patents charge of \$374,000 in the second quarter 2002 that was related to the termination of the peramivir program.

### **Liquidity and Capital Resources**

Cash expenditures have exceeded revenues since the Company's inception. Our operations have principally been funded through various sources, including the following:

- public offerings and private placements of equity and debt securities,

- equipment lease financing,
- facility leases,
- collaborative and other research and development agreements (including licenses and options for licenses),
- research grants and
- interest income.

In addition, we have attempted to contain costs and reduce cash flow requirements by renting scientific equipment and facilities, contracting with other parties to conduct certain research and development and using consultants. We expect to incur additional expenses, potentially resulting in significant losses, as we continue to pursue our research and development activities and undertake additional preclinical studies and clinical trials of compounds which have been or may be discovered. We also expect to incur substantial expenses related to the filing, prosecution, maintenance, defense and enforcement of patent and other intellectual property claims.

On June 25, 2002, we announced we were discontinuing the development of peramivir, our investigational oral influenza neuraminidase inhibitor designed to treat and prevent influenza. After terminating the development of peramivir, the Company streamlined its operations in order to conserve its resources and provide a longer timeframe in which to advance its other programs.

On August 5, 2002, at the request of Dr. Charles E. Bugg, our Chairman and Chief Executive Officer and Dr. J. Claude Bennett, our President, Chief Operating Officer and Medical Director, our Compensation Committee and board of directors approved a 25% reduction in their salaries, effective August 1, 2002. On December 8, 2003, the Compensation Committee and board of directors restored their salaries to the full amount in effect prior to August 1, 2002. This change will be effective on January 1, 2004. In the event of any change of control of the Company, any cumulative salary reductions during the period from August 1, 2002 through December 31, 2003 would become due and payable to them. The aggregate monthly amount of the reduction was \$14,677.

On October 24, 2003, our compensation committee voted to pay Dr. Charles E. Bugg, our Chairman and Chief Executive Officer, \$484,500 as consideration for the cancellation of options held by Dr. Bugg to purchase 170,000 shares of our common stock. The expiration date of the options was November 18, 2003, and the exercise price of the options was \$6.00 per share.

The Company invests its excess cash principally in U.S. marketable securities from a diversified portfolio of institutions with strong credit ratings and in U.S. government and agency bills and notes, and by policy, limits the amount of credit exposure at any one institution. These investments are generally not collateralized and mature within three years. The Company has not realized any losses from such investments. In addition, at September 30, 2003, approximately \$5.4 million was invested in the Merrill Lynch Premier Institutional Fund, which invests primarily in commercial paper, U.S. government and agency bills and notes, corporate notes,



certificates of deposit and time deposits. The Merrill Lynch Premier Institutional Fund is not insured. At September 30, 2003, our cash, cash equivalents and securities held-to-maturity were \$27.6 million, a decrease of \$8.5 million from December 31, 2002, principally due to the funding of current operations.

We have financed some of our equipment purchases with lease lines of credit. We currently have a \$500,000 general line of credit with our bank, secured by a pledge of \$600,000 in marketable securities. There was nothing drawn against this line as of September 30, 2003. In July 2000, we renegotiated our lease for our current facilities, which will expire on June 30, 2010. We have an option to renew the lease for an additional five years at the current market rate in effect on June 30, 2010 and a one-time option to terminate the lease on June 30, 2008 for a termination fee of approximately \$124,000. The lease, as amended effective July 1, 2001 for an additional 7,200 square feet, requires us to pay monthly rent starting at \$33,145 per month in July 2001 and escalating annually to a minimum of \$47,437 per month in the final year, plus our pro rata share of operating expenses and real estate taxes in excess of base year amounts. As part of the lease, we have deposited a U.S. Treasury security in escrow for the payment of rent and performance of other obligations specified in the lease. This pledged amount is currently \$390,000, which will be decreased by \$65,000 annually throughout the term of the lease.

In February 2002, we completed a renovation for approximately \$2.6 million to add two chemistry laboratories and purchase additional equipment. Currently, there are no plans for additional renovations.

As a result of the reduction in our staff during July 2002, we have approximately 14,000 square feet of excess space, which is currently being subleased.

At December 31, 2002, we had long-term operating lease obligations, which provide for aggregate minimum payments of \$580,803 in 2003, \$594,897 in 2004 and \$605,139 in 2005. These obligations include the future rental of our operating facility.

We plan to finance our needs principally from the following:

- our existing capital resources and interest earned on that capital;
- payments under collaborative and licensing agreements with corporate partners; and
- lease or loan financing and future public or private financing.

We believe that our available funds will be sufficient to fund our operations at least through 2004. However, this is a forward looking statement, and there may be changes that would consume available resources significantly before such time. Our long-term capital requirements and the adequacy of our available funds will depend upon many factors, including:

- the progress of our research, drug discovery and development programs;
- changes in existing collaborative relationships;
- our ability to establish additional collaborative relationships;

- the magnitude of our research and development programs;
- the scope and results of preclinical studies and clinical trials to identify drug candidates;
- competitive and technological advances;
- the time and costs involved in obtaining regulatory approvals;
- the costs involved in preparing, filing, prosecuting, maintaining and enforcing patent claims;
- our dependence on others for development and commercialization of our product candidates, and
- successful commercialization of our products consistent with our licensing strategy.

In 2003, our operations have been consuming approximately \$1,000,000 per month, but we expect that our monthly cash used by operations will continue to increase for the next several years. During 2004, we plan to both expand our existing clinical programs and initiate clinical programs for several new disease indications. These additional trials and the related manufacturing, personnel resources and testing required to support these studies will consume significant capital resources and significantly increase our expenses and our net loss. If we proceed fully with the development of these programs, we will need to raise additional capital during 2004 to advance these programs through the development stage to the point of being a candidate for either commercialization or outlicensing.

Additional funding, whether through additional sales of securities or collaborative or other arrangements with corporate partners or from other sources, may not be available when needed or on terms acceptable to us. The issuance of preferred or common stock or convertible securities, with terms and prices significantly more favorable than those of the currently outstanding common stock, could have the effect of diluting or adversely affecting the holdings or rights of our existing stockholders. In addition, collaborative arrangements may require us to transfer certain material rights to such corporate partners. Insufficient funds may require us to delay, scale-back or eliminate certain of our research and development programs.

#### **Critical Accounting Policies**

We have established various accounting policies that govern the application of accounting principles generally accepted in the United States, which were utilized in the preparation of our financial statements. Certain accounting policies involve significant judgments and assumptions by management that have a material impact on the carrying value of certain assets and liabilities; management considers such accounting policies to be critical accounting policies. The judgments and assumptions used by management are based on historical experience and other factors, which are believed to be reasonable under the circumstances. Because of the nature of the judgments and assumptions made by management, actual results could differ from these judgments and estimates, which could have a material impact on the carrying values of assets and liabilities and the results of operations.

We believe the following critical accounting policies affect our more significant judgments and estimates used in the preparation of our financial statements.

### **Revenue Recognition**

The Company recognizes revenue in accordance with SEC Staff Accounting Bulletin No. 101, Revenue Recognition in Financial Statements (“SAB 101”). Research and development revenue on cost-reimbursement agreements is recognized as expenses are incurred, up to contractual limits. Research and development fees, license fees and milestone payments are recognized as revenue when the earnings process is complete, the Company has no further continuing performance obligations and has completed its performance under the terms of the agreement, in accordance with SAB 101. License fees and milestone payments received under licensing agreements that are related to future performance are deferred and taken into income as earned over the estimated drug development period. Recognized revenues and profit are subject to revisions as these contracts or agreements progress to completion. Revisions to revenue or profit estimates are charged to income in the period in which the facts that give rise to the revision become known.

### **Valuation of Financial Instruments**

We carry our held-to-maturity securities at amortized cost, as adjusted for other-than-temporary declines in market value. In determining if and when a decline in market value below amortized cost is other-than-temporary, we evaluate the market conditions and other key measures for our held-to-maturity investments. Future adverse changes in market conditions could result in losses or an inability to recover the carrying value of the held-to-maturity investments that may not be reflected in an investment’s current carrying value, thereby possibly requiring an impairment charge in the future.

### **Deferred Taxes**

We have not had taxable income since incorporation and, therefore, we have not paid any income tax. We have deferred tax assets related to net operating loss carryforwards and research and development carryforwards, and have recorded a valuation allowance to reduce our deferred tax assets to the amount that is more likely than not to be realized. While we have considered future taxable income and ongoing prudent and feasible tax planning strategies in assessing the need for the valuation allowance, in the event we were to determine that we would be able to realize the deferred tax assets in the future in excess of the net recorded amount, an adjustment to the deferred tax asset would increase income in the period such determination was made. Likewise, should we determine that we would not be able to realize all or part of the net deferred tax asset in the future, an adjustment to the deferred tax asset would be charged to income in the period such determination was made.

### **Patents and Licenses**

Patents and licenses are recorded at cost and amortized on a straight-line basis over their estimated useful lives or 20 years, whichever is lesser. These costs are reviewed periodically in accordance with Statement of Financial Accounting Standards No. 144, Accounting for the

Impairment or Disposal of Long-Lived Assets (“Statement No. 144”) to determine any impairment that needs to be recognized.

## Risk Factors

*An investment in our stock involves a high degree of risk. You should consider carefully the following risks, along with all of the other information included in our other filings with the Securities and Exchange Commission, before deciding to buy our common stock. Additional risks and uncertainties not currently known to us or that we currently deem to be immaterial may also impair our business operations. If we are unable to prevent events that have a negative effect from occurring, then our business may suffer. Negative events are likely to decrease our revenue, increase our costs, make our financial results poorer and/or decrease our financial strength, and may cause our stock price to decline. In that case, you may lose all or a part of your investment in our common stock.*

### Risks Relating to Our Business

***We have incurred substantial losses since our inception in 1986, expect to continue to incur such losses and may never be profitable***

Since our inception in 1986, we have not been profitable. We expect to incur additional losses for the foreseeable future, and our losses could increase as our research and development efforts progress. As of September 30, 2003, our accumulated deficit was approximately \$101.4 million. To become profitable, we must successfully develop drug candidates, enter into profitable agreements with other parties and our drug candidates must receive regulatory approval. We or these other parties must then successfully manufacture and market our drug candidates. It could be several years, if ever, before we receive royalties from any future license agreements or revenues directly from product sales.

***If we fail to obtain additional financing, we may be unable to complete the development and commercialization of our product candidates or continue our research and development programs.***

To date, we have financed our operations primarily from sale of our equity securities and, to a lesser extent, revenues from collaborations and interest. In 2003, our operations have been consuming approximately \$1,000,000 per month, but we expect that our monthly cash used by operations will continue to increase for the next several years. During 2004, we plan to both expand our existing clinical programs and initiate clinical programs for several new disease indications. These additional trials and the related manufacturing, personnel resources and testing required to support these studies will consume significant capital resources and significantly increase our expenses and our net loss.

If we proceed fully with the development of these programs, we will need to raise additional capital during 2004 to advance these programs through the development stage to the point of being a candidate for either commercialization or outlicensing. Our long-term capital requirements and the adequacy of our available funds will depend upon many factors, including:

- the progress of our research, drug discovery and development programs;
- changes in existing collaborative relationships;

- our ability to establish additional collaborative relationships;
- the magnitude of our research and development programs;
- the scope and results of preclinical studies and clinical trials to identify drug candidates;
- competitive and technological advances;
- the time and costs involved in obtaining regulatory approvals;
- the costs involved in preparing, filing, prosecuting, maintaining and enforcing patent claims;
- our dependence on others for development and commercialization of our product candidates; and
- successful commercialization of our products consistent with our licensing strategy.

We will be required to raise additional capital to complete the development and commercialization of our current product candidates. Additional funding, whether through additional sales of securities or collaborative or other arrangements with corporate partners or from other sources, may not be available when needed or on terms acceptable to us. The issuance of preferred or common stock or convertible securities, with terms and prices significantly more favorable than those of the currently outstanding common stock, could have the effect of diluting or adversely affecting the holdings or rights of our existing stockholders. In addition, collaborative arrangements may require us to transfer certain material rights to such corporate partners. Insufficient funds may require us to delay, scale-back or eliminate certain of our research and development programs.

***We have not commercialized any products or technologies and our future revenue generation is uncertain***

We have not yet commercialized any products or technologies, and we may never be able to do so. Our revenue from collaborative agreements is dependent upon the status of our preclinical and clinical programs. If we fail to advance these programs to the point of being able to enter into successful collaborations, we will not receive any future milestone or other collaborative payments.

Any future revenue directly from product sales would depend on our ability to successfully complete clinical studies, obtain regulatory approvals, manufacture, market and commercialize any approved drugs.

***If our development collaborations with other parties fail, the development of our drug candidates will be delayed or stopped***

We rely heavily upon other parties for many important stages of our drug development programs, including:

- discovery of proteins that cause or enable biological reactions necessary for the progression of the disease or disorder, called enzyme targets;
- license or design enzyme inhibitors for development as drug candidates;
- execution of some preclinical studies and late-stage development for our compounds and drug candidates;
- management of our clinical trials, including medical monitoring and data management;
- management of our regulatory function; and
- manufacturing, sales, marketing and distribution of our drug candidates.

Our failure to engage in successful collaborations at any one of these stages would greatly impact our business. If we do not license enzyme targets or inhibitors from academic institutions or from other biotechnology companies on acceptable terms, our product development efforts would suffer. Similarly, if the contract research organizations that conduct our initial or late-stage clinical trials or manage our regulatory function breached their obligations to us, this would delay or prevent the development of our drug candidates.

Even more critical to our success is our ability to enter into successful collaborations for the late-stage clinical development, regulatory approval, manufacturing, marketing, sales and distribution of our drug candidates. Our general strategy is to rely upon other parties for all of these steps so that we can focus exclusively on the key areas of our expertise. For some smaller niche markets, we may perform these steps ourselves and outsource those functions where we do not have the internal expertise. This heavy reliance upon third parties for these critical functions presents several risks, including:

- these contracts may expire or the other parties to the contract may terminate them;
- our partners may choose to pursue alternative technologies, including those of our competitors;
- we may have disputes with a partner that could lead to litigation or arbitration;
- our partners may not devote sufficient capital or resources towards our drug candidates; and
- our partners may not comply with applicable government regulatory requirements.

Any problems encountered with our current or future partners could delay or prevent the development of our compounds, which would severely affect our business, because if our compounds do not reach the market in a timely manner, or at all, we may never receive any milestone, product or royalty payments.

***If the clinical trials of our drug candidates fail, our drug candidates will not be marketed, which would result in a complete absence of product related revenue***

To receive the regulatory approvals necessary for the sale of our drug candidates, we or our licensees must demonstrate through preclinical studies and clinical trials that each drug candidate is safe and effective. If we or our licensees are unable to demonstrate that our drug candidates are safe and effective, our drug candidates will not receive regulatory approval and will not be marketed, which would result in a complete absence of product related revenue. The clinical trial process is complex and uncertain. Because of the cost and duration of clinical trials, we may decide to discontinue development of product candidates that are either unlikely to show good results in the trials or unlikely to help advance a product to the point of a meaningful collaboration. Positive results from preclinical studies and early clinical trials do not ensure positive results in clinical trials designed to permit application for regulatory approval, called pivotal clinical trials. We may suffer significant setbacks in pivotal clinical trials, even after earlier clinical trials show promising results. Any of our drug candidates may produce undesirable side effects in humans. These side effects could cause us or regulatory authorities to interrupt, delay or halt clinical trials of a drug candidate. These side effects could also result in the FDA or foreign regulatory authorities refusing to approve the drug candidate for any targeted indications. We, our licensees, the FDA or foreign regulatory authorities may suspend or terminate clinical trials at any time if we or they believe the trial participants face unacceptable health risks. Clinical trials may fail to demonstrate that our drug candidates are safe or effective.

Clinical trials are lengthy and expensive. We or our licensees incur substantial expense for, and devote significant time to, preclinical testing and clinical trials, yet cannot be certain that the tests and trials will ever result in the commercial sale of a product. For example, clinical trials require adequate supplies of drug and sufficient patient enrollment. Delays in patient enrollment can result in increased costs and longer development times. Even if we or our licensees successfully complete clinical trials for our product candidates, we or our licensees might not file the required regulatory submissions in a timely manner and may not receive regulatory approval for the drug candidate.

***If we or our licensees do not obtain and maintain governmental approvals for our products under development, we or our partners will not be able to sell these potential products, which would significantly harm our business because we will receive no revenue***

We or our licensees must obtain regulatory approval before marketing or selling our future drug products. If we or our licensees are unable to receive regulatory approval and do not market or sell our future drug products, we will never receive any revenue from such product sales. In the United States, we or our partners must obtain FDA approval for each drug that we intend to commercialize. The FDA approval process is typically lengthy and expensive, and approval is never certain. Products distributed abroad are also subject to foreign government regulation. The FDA or foreign regulatory agencies have not approved any of our drug candidates. If we or our licensees fail to obtain regulatory approval we will be unable to market and sell our future drug products. We have several drug products in various stages of preclinical and clinical development; however, we are unable to determine when, if ever, any of these products will be commercially available. Because of the risks and uncertainties in biopharmaceutical development, our drug candidates could take a significantly longer time to



gain regulatory approval than we expect or may never gain approval. If the FDA delays regulatory approval of our drug candidates, our management's credibility, our company's value and our operating results may suffer. Even if the FDA or foreign regulatory agencies approve a drug candidate, the approval may limit the indicated uses for a drug candidate and/or may require post-marketing studies.

The FDA regulates, among other things, the record keeping and storage of data pertaining to potential pharmaceutical products. We currently store most of our preclinical research data at our facility. While we do store duplicate copies of most of our clinical data offsite, we could lose important preclinical data if our facility incurs damage. If we get approval to market our potential products, whether in the United States or internationally, we will continue to be subject to extensive regulatory requirements. These requirements are wide ranging and govern, among other things:

- adverse drug experience reporting regulations;
- product promotion;
- product manufacturing, including good manufacturing practice requirements; and
- product changes or modifications.

Our failure to comply with existing or future regulatory requirements, or our loss of, or changes to, previously obtained approvals, could have a material adverse effect on our business because we will not receive product or royalty revenues if we or our licensees do not receive approval of our products for marketing.

In June 1995, we notified the FDA that we submitted incorrect data for our Phase II studies of BCX-34 applied to the skin for cutaneous T-cell lymphoma and psoriasis. The FDA inspected us in November 1995 and issued us a List of Inspectional Observations, Form FDA 483, which cited our failure to follow good clinical practices. The FDA also inspected us in June 1996. The focus was on the two 1995 Phase II dose-ranging studies of topical BCX-34 for the treatment of cutaneous T-cell lymphoma and psoriasis. As a result of the investigation, the FDA issued us a Form FDA 483, which cited our failure to follow good clinical practices. BioCryst is no longer developing BCX-34; however, as a consequence of these two investigations, our ongoing and future clinical studies may receive increased scrutiny, which may delay the regulatory review process.

***We may be unable to establish sales, marketing and distribution capabilities necessary to successfully commercialize products we may successfully develop***

We currently have no marketing capability and no direct or third-party sales or distribution capabilities. If we successfully develop a drug candidate and decide to commercialize it ourselves rather than relying on third parties, we may be unable to establish marketing, sales and distribution capabilities necessary to commercialize and gain market acceptance for that product.

***If our drug candidates do not achieve broad market acceptance, our business may never become profitable***

Our drug candidates may not gain the market acceptance required for us to be profitable even if they successfully complete initial and final clinical trials and receive approval for sale by the FDA or foreign regulatory agencies. The degree of market acceptance of any drug candidates that we or our partners develop will depend on a number of factors, including:

- cost-effectiveness of our drug candidates;
- their safety and effectiveness relative to alternative treatments;
- reimbursement policies of government and third-party payers; and
- marketing and distribution support for our drug candidates.

Physicians, patients, payers or the medical community in general may not accept or use our drug candidates even after the FDA or foreign regulatory agencies approve the drug candidates. If our drug candidates do not achieve significant market acceptance, we will not have enough revenues to become profitable.

***We face intense competition, and if we are unable to compete effectively, the demand for our products, if any, may be reduced***

The biotechnology and pharmaceutical industries are highly competitive and subject to rapid and substantial technological change. We face, and will continue to face, competition in the licensing of desirable disease targets, licensing of desirable drug candidates, and development and marketing of our product candidates from academic institutions, government agencies, research institutions and biotechnology and pharmaceutical companies. Competition may also arise from, among other things:

- other drug development technologies;
- methods of preventing or reducing the incidence of disease, including vaccines; and
- new small molecule or other classes of therapeutic agents.

Developments by others may render our product candidates or technologies obsolete or noncompetitive.

We are performing research on or developing products for the treatment of several disorders including T-cell mediated disorders (T-cell cancers, psoriasis, and rheumatoid arthritis), cardiovascular, oncology, and hepatitis C, and there are a number of competitors to products in our research pipeline. If one or more of our competitors' products or programs are successful, the market for our products may be reduced or eliminated.

Compared to us, many of our competitors and potential competitors have substantially greater:

- capital resources;
- research and development resources, including personnel and technology;
- regulatory experience;
- preclinical study and clinical testing experience;
- manufacturing and marketing experience; and
- production facilities.

Any of these competitive factors could reduce demand for our products.

***If we fail to adequately protect or enforce our intellectual property rights or secure rights to patents of others, the value of those rights would diminish***

Our success will depend in part on our ability and the abilities of our licensors to obtain patent protection for our products, methods, processes and other technologies to preserve our trade secrets, and to operate without infringing the proprietary rights of third parties. If we or our partners are unable to adequately protect or enforce our intellectual property rights for our products, methods, processes and other technologies, the value of the drug candidates that we license to derive revenue would diminish. Additionally, if our products, methods, processes and other technologies infringe the proprietary rights of other parties, we could incur substantial costs. The U.S. Patent and Trademark Office has issued to us a number of U.S. patents for our various inventions and we have in-licensed several patents from various institutions. We have filed additional patent applications and provisional patent applications with the U.S. Patent and Trademark Office. We have filed a number of corresponding foreign patent applications and intend to file additional foreign and U.S. patent applications, as appropriate. We cannot assure you as to:

- the degree and range of protection any patents will afford against competitors with similar products;
- if and when patents will issue; or
- whether or not others will obtain patents claiming aspects similar to those covered by our patent applications.

If the U.S. Patent and Trademark Office upholds patents issued to others or if the U.S. Patent and Trademark Office grants patent applications filed by others, we may have to:

- obtain licenses or redesign our products or processes to avoid infringement;
- stop using the subject matter claimed in those patents; or
- pay damages.

We may initiate, or others may bring against us, litigation or administrative proceedings related to intellectual property rights, including proceedings before the U.S. Patent and Trademark Office. Any judgment adverse to us in any litigation or other proceeding arising in connection with a patent or patent application could materially and adversely affect our business, financial condition and results of operations. In addition, the costs of any such proceeding may be substantial whether or not we are successful.

Our success is also dependent upon the skills, knowledge and experience, none of which is patentable, of our scientific and technical personnel. To help protect our rights, we require all employees, consultants, advisors and collaborators to enter into confidentiality agreements that prohibit the disclosure of confidential information to anyone outside of our company and require disclosure and assignment to us of their ideas, developments, discoveries and inventions. These agreements may not provide adequate protection for our trade secrets, know-how or other proprietary information in the event of any unauthorized use or disclosure or the lawful development by others of such information, and if any of our proprietary information is disclosed, our business will suffer because our revenues depend upon our ability to license our technology and any such events would significantly impair the value of such a license.

***If we fail to retain our existing key personnel or fail to attract and retain additional key personnel, the development of our drug candidates and the expansion of our business will be delayed or stopped***

We are highly dependent upon our senior management and scientific team, the loss of whose services might impede the achievement of our development and commercial objectives. Competition for key personnel with the experience that we require is intense and is expected to continue to increase. Our inability to attract and retain the required number of skilled and experienced management, operational and scientific personnel, will harm our business because we rely upon these personnel for many critical functions of our business. In addition, we rely on members of our scientific advisory board and consultants to assist us in formulating our research and development strategy. All of the members of the scientific advisory board and all of our consultants are otherwise employed and each such member or consultant may have commitments to other entities that may limit their availability to us.

***If users of our drug products are not reimbursed for use, future sales of our drug products will decline***

The lack of reimbursement for the use of our product candidates by hospitals, clinics, patients or doctors will harm our business. Medicare, Medicaid, health maintenance organizations and other third-party payers may not authorize or otherwise budget for the reimbursement of our products. Governmental and third-party payers are increasingly challenging the prices charged for medical products and services. We cannot be sure that third-party payers would view our product candidates as cost-effective, that reimbursement will be available to consumers or that reimbursement will be sufficient to allow our product candidates to be marketed on a competitive basis. Changes in reimbursement policies, or attempts to contain costs in the health care industry could limit or restrict reimbursement for our product candidates and would materially and adversely affect our business, because future product sales would decline and we would receive less product or royalty revenue.

***If we face clinical trial liability claims related to the use or misuse of our compounds in clinical trials, our management's time will be diverted and we will incur litigation costs***

We face an inherent business risk of liability claims in the event that the use or misuse of our compounds results in personal injury or death. We have not experienced any clinical trial liability claims to date, but we may experience these claims in the future. After commercial introduction of our products we may experience losses due to product liability claims. We currently maintain clinical trial liability insurance coverage in the amount of \$5.0 million per occurrence and \$5.0 million in the aggregate, with an additional \$2.0 million potentially available under our umbrella policy. The insurance policy may not be sufficient to cover claims that may be made against us. Clinical trial liability insurance may not be available in the future on acceptable terms, if at all. Any claims against us, regardless of their merit, could materially and adversely affect our financial condition, because litigation related to these claims would strain our financial resources in addition to consuming the time and attention of our management.

***If our computer systems fail, our business will suffer***

Our drug development activities depend on the security, integrity and performance of the computer systems supporting them, and the failure of our computer systems could delay our drug development efforts. We currently store most of our preclinical and clinical data at our facility. Duplicate copies of all critical data are stored off-site in a bank vault. Any significant degradation or failure of our computer systems could cause us to inaccurately calculate or lose our data. Loss of data could result in significant delays in our drug development process and any system failure could harm our business and operations.

***If, because of our use of hazardous materials, we violate any environmental controls or regulations that apply to such materials, we may incur substantial costs and expenses in our remediation efforts***

Our research and development involves the controlled use of hazardous materials, chemicals and various radioactive compounds. We are subject to federal, state and local laws and regulations governing the use, storage, handling and disposal of these materials and some waste products. Accidental contamination or injury from these materials could occur. In the event of an accident, we could be liable for any damages that result and any liabilities could exceed our resources. Compliance with environmental laws and regulations could require us to incur substantial unexpected costs, which would materially and adversely affect our results of operations.

#### **Risks Relating to Our Common Stock**

***Our stock price is likely to be highly volatile and the value of your investment could decline significantly***

The market prices for securities of biotechnology companies in general have been highly volatile and may continue to be highly volatile in the future. Moreover, our stock price has fluctuated frequently, and these fluctuations are often not related to our financial results. For the twelve months ended September 30, 2003, the 52-week range of the market price of our stock

has been from \$0.82 to \$7.37 per share. The following factors, in addition to other risk factors described in this section, may have a significant impact on the market price of our common stock:

- announcements of technological innovations or new products by us or our competitors;
- developments or disputes concerning patents or proprietary rights;
- status of new or existing licensing or collaborative agreements;
- we or our licensees achieving or failing to achieve development milestones;
- publicity regarding actual or potential medical results relating to products under development by us or our competitors;
- regulatory developments in both the United States and foreign countries;
- public concern as to the safety of pharmaceutical products;
- actual or anticipated fluctuations in our operating results;
- changes in financial estimates or recommendations by securities analysts;
- economic and other external factors or other disasters or crises; and
- period-to-period fluctuations in our financial results.

***Because stock ownership is concentrated, you and other investors will have minimal influence on stockholder decisions***

As of November 30, 2003, our directors, executive officers and some principal stockholders and their affiliates, including Johnson & Johnson Development Corporation, beneficially owned approximately 40.4% (directors and officers owned 28.2%) of our outstanding common stock and common stock equivalents. As a result, these holders, if acting together, are able to significantly influence matters requiring stockholder approval, including the election of directors. This concentration of ownership may delay, defer or prevent a change in our control.

***We have anti-takeover provisions in our corporate charter documents that may result in outcomes with which you do not agree***

Our board of directors has the authority to issue up to 3,178,500 shares of undesignated preferred stock and to determine the rights, preferences, privileges and restrictions of those shares without further vote or action by our stockholders. The rights of the holders of any preferred stock that may be issued in the future may adversely affect the rights of the holders of common stock. The issuance of preferred stock could make it more difficult for third parties to acquire a majority of our outstanding voting stock.

In addition, our certificate of incorporation provides for staggered terms for the members of the board of directors and supermajority approval of the removal of any member of the board of directors and prevents our stockholders from acting by written consent. Our certificate also requires supermajority approval of any amendment of these provisions. These provisions and other provisions of our by-laws and of Delaware law applicable to us could delay or make more difficult a merger, tender offer or proxy contest involving us.

In June 2002, our board of directors adopted a stockholder rights plan and, pursuant thereto, issued preferred stock purchase rights (“Rights”) to the holders of our common stock. The Rights have certain anti-takeover effects. If triggered, the Rights would cause substantial dilution to a person or group of persons who acquires more than 15% (19.9% for William W. Featheringill, a Director who already owns more than 15%) of our common stock on terms not approved by the board of directors.

***We Have Never Paid Dividends on Our Common Stock and Do Not Anticipate Doing So in the Foreseeable Future***

We have never paid cash dividends on our stock. We currently intend to retain all future earnings, if any, for use in the operation of our business. Accordingly, we do not anticipate paying cash dividends on our common stock in the foreseeable future.

**Information Regarding Forward-Looking Statements**

This discussion contains forward-looking statements, which are subject to risks and uncertainties. These forward-looking statements can generally be identified by the use of words such as “may,” “will,” “intends,” “plans,” “believes,” “anticipates,” “expects,” “estimates,” “predicts,” “potential,” the negative of these words or similar expressions. Statements that describe our future plans, strategies, intentions, expectations, objectives, goals or prospects are also forward-looking statements. Discussions containing these forward-looking statements are principally contained in “Business” and “Management’s Discussion and Analysis of Financial Condition and Results of Operations” above, as well as any amendments we make to those sections in filings with the SEC.

These statements reflect our current views with respect to future events and are based on assumptions and subject to risks and uncertainties which may cause our actual results, performance or achievements to be materially different from any future results, performances or achievements expressed or implied by the forward-looking statements. Given these uncertainties, you should not place undue reliance on these forward-looking statements. We discuss many of these risks in greater detail in “Risk Factors.” Also, these forward-looking statements represent our estimates and assumptions only as of the date of this document.

You should read this discussion completely and with the understanding that our actual future results may be materially different from what we expect. We may not update these forward-looking statements, even though our situation may change in the future. We qualify all of our forward-looking statements by these cautionary statements.