Gentium S.p.A.
Form 20-F
March 31, 2011
As filed with the Securities and Exchange Commission on March 31, 2011

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, D.C. 20549

FORM 20-F

¨REGISTRATION STATEMENT PURSUANT TO SECTION 12(b) OR (g) OF THE SECURITIES EXCHANGE ACT OF 1934

OR

þANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
For the Fiscal Year Ended: December 31, 2010

OR

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

OR

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

000-51341
(Commission file number)

GENTIUM S.p.A.
(Exact Name of Registrant as Specified in its Charter)
NOT APPLICABLE
(Translation of Registrant's Name into English)

Italy
(Jurisdiction of incorporation or organization)

Piazza XX Settembre 2
22079 Villa Guardia (Como), Italy
+39 031 385111
(Address, including zip code, and telephone number,
including area code, of Registrant's principal executive offices)

Securities registered or to be registered pursuant to Section 12(b) of the Act.

Title of each class	Name of each exchange on which registered

American Depositary Shares	The Nasdaq Global Market
Ordinary shares, no par value*	The Nasdaq Global Market

(Title of Class)

Securities registered or to be registered pursuant to Section 12(g) of the Act: None

Securities for which there is a reporting obligation pursuant to Section 15(d) of the Act: None

Indicate the number of outstanding shares of each of the issuer's classes of capital or common stock as of the close of the period covered by the annual report.

14,956,317 ordinary shares

- Not for trading, but only in connection with the registration of the American Depositary Shares.

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act.

Yes ¨ No þ

If this report is an annual or transition report, indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934.

Yes ¨ No þ

Note – Checking the box above will not relieve any registrant required to file reports pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934 from their obligations under those Sections.

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days.

Yes þ No ¨

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files).

Yes ¨ No þ

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

Large accelerated filer ¨ Accelerated filer ¨ Non-accelerated filer þ

Indicate by check mark which basis of accounting the registrant has used to prepare the financial statements included in this filing:

U.S. GAAP þ International Financial Reporting Standards as issued by the International Accounting Standards Board ¨ Other ¨

If "Other has been checked in response to the previous question, indicated by check mark which financial item the registrant has elected to follow.

Yes ¨ No ¨

If this is an annual report, indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act).

Yes ¨ No þ

TABLE OF CONTENTS

PART I

ITEM 1. IDENTITY OF DIRECTORS, SENIOR MANAGEMENT AND ADVISERS

Not applicable.

ITEM 2. OFFER STATISTICS AND EXPECTED TIMETABLE

Not applicable.

ITEM 3. KEY INFORMATION

GENTIUM S.P.A.

We are a biopharmaceutical company focused on the development and manufacture of our primary product candidate, defibrotide, an investigational drug based on a mixture of single-stranded and double-stranded DNA extracted from pig intestines. Our development of defibrotide has been focused on the treatment and prevention of a disease called hepatic veno-occlusive disease, or VOD, a condition that occurs when veins in the liver are blocked as a result of cancer treatments, such as chemotherapy or radiation, that are administered prior to stem cell transplantation. Severe VOD is the most extreme form of VOD and is linked to multiple-organ failure and high rates of morbidity and mortality.

We have completed two clinical trials, a Phase III trial of defibrotide for the treatment of severe VOD in the U.S., Canada and Israel and a Phase II/III pediatric trial in Europe for the prevention of VOD. Defibrotide has been given "orphan" status by the U.S. Food and Drug Agency, or FDA, and the European Medicines Agency, or EMA, which means that we will have limited market exclusivity upon regulatory approval. Defibrotide has also been granted "fast-track product" designation by the FDA for the treatment of VOD. While we have not yet obtained regulatory approval to market defibrotide, we are authorized to distribute defibrotide on a pre-approval basis under a treatment Investigational New Drug, or IND, protocol, which we call our cost recovery program, in the U.S. and through a named-patient program throughout the rest of the world. We do not know of any FDA or EMA approved treatments for VOD.

We have completed certain preclinical and clinical studies requested by regulatory authorities. As part of our overall strategy, we anticipate filing for regulatory approval for defibrotide in the U.S. and Europe by the end of our second quarter in 2011. We are also working on our U.S. regulatory strategy with our commercial partner, Sigma-Tau Finanziaria S.p.A. and its affiliate, Sigma-Tau Pharmaceuticals, Inc., to which we have licensed our commercial rights to use defibrotide for both the treatment and prevention of VOD in the Americas. We are currently establishing our European sales force, as we intend to commercialize defibrotide in the major European countries on our own.

We have a manufacturing plant in Italy where we produce active pharmaceutical ingredients, which are subsequently used to make the finished forms of various drugs. We believe that we are the sole worldwide producer of defibrotide. In addition to defibrotide, we manufacture urokinase and sulglicotide, both of which are sold to third parties. All of the Company's operating assets are located in Italy.

We have accumulated a deficit of approximately €95.6 million since our inception. In 2010, we have been cash flow positive, primarily due to the upfront payment received from Sigma-Tau Pharmaceuticals, Inc. in connection with the expansion of the license for defibrotide in the Americas, together with revenue generated from the cost recovery and named-patient programs. However, if we are unable to obtain regulatory approval to commercialize defibrotide, unable to continue to generate sufficient revenue through our cost recovery and named-patient programs, or if we are

required to fund additional clinical trials, we may revert to operating losses.

We are subject to a number of risks, including our ability to successfully obtain regulatory approval for defibrotide, the uncertainty that defibrotide will become a successful commercial product, our ability to generate projected revenue through our named-patient and cost recovery programs, our dependence on corporate partners, our ability to obtain financing, if necessary, and potential changes in the health care industry. The risks we face are described in more detail under "Risk Factors" in this annual report. The risks described are not the only risks we face. Additional risks not presently known to us or that we currently deem immaterial may also impair our business operations. Our business, financial condition and operations could be materially adversely affected by any of these risks. The trading price of our securities could decline as a result of any of these risks and you may lose all or part of your investment. The discussion of risks includes or refers to forward-looking statements; you should read the explanation of the qualifications and limitations on such forward-looking statements discussed elsewhere in this annual report.

SELECTED FINANCIAL DATA

The following selected financial data should be read in conjunction with "Operating and Financial Review and Prospects" and our financial statements and the related notes appearing elsewhere in this annual report. The selected financial data as of December 31, 2009 and December 31, 2010 and for the three years ended December 31, 2010 are derived from our audited financial statements, which are included in this annual report. The selected financial data as of December 31, 2006, December 31, 2007 and December 31, 2008 and for the years ended December 31, 2006 and December 31, 2007 are derived from our audited financial statements, which are not included in this annual report. Our historical results are not necessarily indicative of results to be expected in any future period.

The convenience translation into U.S. dollars is solely for the benefit of the reader, and does not imply that our results would actually have been these amounts in U.S. dollars had the U.S. dollar been our functional currency.

Statement of Operations Data: (000s omitted except per share data)	For the Years Ended December 31,					
	2006	2007	2008	2009	2010	2010(1)
Revenues:						
Product sales to related party	€3,754	€2,704	€651	€195	€-	$-
Product sales to third parties	321	2,390	4,792	9,507	19,715	26,160
Total product sales	4,075	5,094	5,443	9,702	19,715	26,160
Other revenues	109	15	25	129	289	383
Other revenues from related party	140	2,500	1,970	337	4,547	6,033
Total revenues	4,324	7,609	7,438	10,168	24,551	32,576
Operating costs and expenses:						
Cost of goods sold	3,092	4,584	5,596	4,002	5,786	7,677
Charges from related parties	854	748	537	279	346	459
Research and development	8,927	14,497	9,569	3,512	6,104	8,099
General and administrative	5,421	6,279	7,668	6,036	5,835	7,742
Restructuring charges	-	-	-	-	1,101	1,461
Depreciation and amortization	261	725	998	916	908	1,205
Write-down of assets	-	13,740	3,403	-	-	-
	18,555	40,573	27, 771	14,745	20,080	26,643
Operating income/(loss)	(14,231)	(32,964)	(20,333)	(4,577)	4,471	5,933
Foreign currency exchange gain (loss), net	(627)	(4,001)	173	162	90	119
Interest income/(expense), net	490	1,357	256	(110)	(87)	(115)
Pre-tax income/(loss)	(14,368)	(35,608)	(19,904)	(4,525)	4,474	5,937
Income tax expense:						
Current	-	-	-	-	(397)	(527)
	-	-	-	-	(397)	(527)
Net income/(loss)	€(14,368)	€(35,608)	€(19,904)	€(4,525)	€4,077	$5,410
Net income/(loss) per share:						

Basic and Diluted	€(1.33)	€(2.52)	€(1.33)	€(0.30)	€0.27	$0.36

(1) Euro amounts are translated into U.S. dollars using the Noon Buying Rate for the Euro on December 30, 2010, of U.S. $1.3269 per Euro. No representation is made that the Euro amounts referred to in this annual report could have been or could be converted into U.S. dollars at any particular rate or at all.

The following table summarizes certain of our balance sheet data.

(000s omitted except per share d share data	2006	2007	2008	2009	2010	2010(1)
Balance Sheet Data:						
Cash and cash equivalent	€10,205	€25,964	€11,491	€1,392	€8,742	$11,600
Working capital	13,543	19,002	3,152	1,041	6,555	8,698
Property, net	9,424	11,544	10,751	9,717	8,598	11,409
Total assets	35,393	51,959	26,901	18,167	24,674	32,740
Long-term debt, net of current maturities	5,683	4,421	3,268	3,098	1,759	2,334
Shareholders' equity	21,687	28,359	10,451	7,330	12,930	17,157
Capital stock	€11,774	€14,946	€14,956	€106,962	€108,485	$143,949
Number of shares	11,773,613	14,946,317	14,956,317	14,956,317	14,956,317	14,956,317

(1) Euro amounts are translated into U.S. dollars using the Noon Buying Rate for the Euro on December 30, 2010, of U.S. $1.3269 per Euro. No representation is made that the Euro amounts referred to in this annual report could have been or could be converted into U.S. dollars at any particular rate or at all.

Exchange Rate Information

Fluctuations in the exchange rates between the Euro and the U.S. dollar will affect the U.S. dollar amounts received by owners of ADSs on conversion by the depositary of dividends, if any, paid in euros on the ordinary shares represented by the ADSs. Moreover, such fluctuations may also affect the U.S. dollar price of the ADSs on the Nasdaq Global Market. The following table sets forth information regarding the exchange rates of U.S. dollars per Euro for the periods indicated, calculated by using the average of the noon buying rates on the last day of each month during the periods presented.

	U.S. Dollar per Euro	
Year	Average	Period End
2006	1.2661	1.3197
2007	1.3797	1.4603
2008	1.4695	1.3919
2009	1.3935	1.4332
2010	1.3221	1.3269

Source: Federal Reserve Statistical Releases H.10 and G.5

The following table sets forth information regarding the high and low exchange rates of U.S. dollars per Euro for the periods indicated based on the noon buying rate on each day of such period.

	U.S. Dollar per Euro	
Month	High	Low
September 2010	1.3638	1.2708
October 2010	1.4066	1.3754
November 2010	1.4224	1.3036
December 2010	1.3395	1.3101
January 2011	1.3715	1.2944
February 2011	1.3794	1.3474
March 2011 (through March 25, 2011)	1.4212	1.3813

Source: Federal Reserve Statistical Release H.10

On March 25, 2011, the noon buying rate was €1.00 to $1.4144

We use the Euro as our functional currency for financial reporting. This annual report contains translations of euros into U.S. dollars at specified rates solely for the convenience of the reader. No representation is made that the Euro amounts referred to in this annual report could have been or could be converted into U.S. dollars at any particular rate or at all.

CAPITALIZATION AND INDEBTEDNESS

Not applicable.

REASONS FOR THE OFFER AND USE OF PROCEEDS

Not applicable.

RISK FACTORS

You should carefully consider the risks described below, in conjunction with the other information and financial statements and related notes included elsewhere in this annual report, before making an investment decision. You should pay particular attention to the fact that we conduct our operations in Italy and are governed by a legal and regulatory environment that in some respects differs significantly from the environment that prevails in other countries with which you may be familiar. Our business, financial condition or results of operations could be affected materially and adversely by any or all of these risks. In that event, the market price of our ADSs could decline and you could lose all or part of your investment.

Risks Relating to Our Business

We may not be able to meet our future cash requirements without obtaining additional capital from external sources.

As of December 31, 2010, we had approximately €8.7 million in cash and cash equivalents. We have generated a significant portion of our revenue through the distribution of our primary product candidate, defibrotide, on a pre-approval basis under a treatment IND protocol, which we call our cost recovery program, in the U.S, and through a named-patient program throughout the rest of the world. Prior to the initiation of these compassionate use programs in 2009, we had only generated net losses. We do not know how much longer we will be able to distribute defibrotide through these compassionate use programs.

We expect that existing cash and cash equivalents with respect to the anticipated cash flow from product sales will be sufficient to support our current operation for at least the next twelve months. We will need additional funds if our cash requirements exceed our current expectation or if we generate less revenue than we expect. Historically, we have financed our operations primarily through the sale of equity and convertible notes, interest income earned on cash and cash equivalents, and debt provided through secured lines of credit. If we raise additional funds through the issuance of equity or convertible debt securities, the percentage ownership of our stockholders could be significantly diluted, and these newly-issued securities may have rights, preferences or privileges senior to those of existing stockholders. If we obtain additional debt financing, a substantial portion of our operating cash flow may be dedicated to the payment of principal and interest on such indebtedness, and the terms of the debt securities issued could impose significant restrictions on our operations. To the extent that we are required to obtain additional capital through equity and/or debt financings, loans or collaborative arrangements with corporate partner, we may not be available to us on favorable terms, if at all.

Our failure to raise additional funds in the future may delay the development of defibrotide.

The development of defibrotide has required a commitment of substantial funds and we may need to commit a substantial amount of additional funds in order to obtain regulatory approval to market and commercialize defibrotide.

Our future capital requirements are dependent upon many factors, some of which are beyond our control, including:

- the successful and continued development of defibrotide in preclinical and clinical testing in existing and any required future clinical trials;
- the costs associated with protecting and expanding our patent and other intellectual property rights;
- future payments, if any, received or made under existing or possible future collaborative arrangements;
- the costs associated with building a future commercial infrastructure;

- the costs associated with implementing any upgrades to our manufacturing facility as required by the FDA, EMA, or other regulatory body;
- the timing and cost to develop and obtain regulatory approvals to market defibrotide;
- success of our named-patient and cost recovery programs;
- market acceptance of defibrotide; and
- the overall condition of the financial markets.

We cannot assure you that funds will be available to us in the future on favorable terms, if at all. If adequate funds are not available to us on terms that we find acceptable, or at all, we may be required to delay, reduce the scope of, or eliminate research and development efforts on defibrotide. We may also be forced to curtail, cease or restructure our operations, obtain funds by entering into arrangements with collaborators on unattractive terms or relinquish rights to defibrotide that we would not otherwise relinquish in order to continue independent operations.

While we have started to generate limited revenues from sales of defibrotide, we have had significant losses to date and we do not know whether we will ever generate significant revenues.

We have generated net losses since our inception. While we have generated revenues through commercial sales of our active pharmaceutical ingredients and, recently, through sales of defibrotide on a pre-approval basis via our named-patient and cost recovery programs, we may revert to incurring significant losses, particularly if we are required to perform additional clinical trials and testing and regulatory compliance activities, or if we unable to continue to distribute defibrotide on a pre-approval basis. If we incur operating losses for longer than we expect and/or we are unable to raise additional capital, we may become insolvent and unable to continue our operations.

Our current ability to continue as a going concern is largely dependent on the revenues being generated from the distribution of defibrotide on a pre-approval basis through our named-patient and cost recovery programs. If we fail to generate projected revenues from these compassionate use programs, we may be unable to reduce our expenses quickly enough to compensate for the shortfall, and we may then need to obtain additional capital through equity or debt financings, loans and collaborative agreements with corporate partners, which may not be available to us on favorable terms, if at all. In addition, our fluctuating operating results may fail to meet the expectations of investors, which may cause the price of our ADSs to decline.

Even if we are successful in obtaining regulatory approval to market defibrotide, we may have very limited markets and may not generate enough revenues from defibrotide to fund our business. The FDA and EMA have designated defibrotide to treat severe VOD and defibrotide to prevent VOD, as “orphan drugs,” which generally means that fewer than 200,000 people are affected by the disease or condition. In addition, our long-term ability to generate cash from operations is dependent in part on the success of our current strategic partner, Sigma-Tau Pharmaceuticals, Inc., to commercialize defibrotide.

We currently do not have any regulatory approvals to sell defibrotide to treat or prevent VOD, and we cannot guarantee that we will be able to sell defibrotide to treat or prevent VOD anywhere in the world.

Currently, we are required in both the United States and in foreign countries to obtain approval from those countries' regulatory authorities before we can manufacture (or have third-party manufacturers produce), market and sell defibrotide in those countries. The FDA and other United States and foreign regulatory agencies have substantial authority to require additional testing and to delay or withhold registration and marketing approval of our product candidates.

Obtaining regulatory approval has been and continues to be increasingly difficult and costly and takes many years, and, once obtained, is costly to maintain. With the occurrence of a number of high profile safety events with certain pharmaceutical products, regulatory authorities, and in particular the FDA, members of Congress, the United States Government Accountability Office (GAO), Congressional committees, private health/science foundations and organizations, medical professionals, including physicians and investigators, and the general public are increasingly concerned about potential or perceived safety issues associated with pharmaceutical and biological products, whether under study for initial approval or already marketed.

This increasing concern has produced greater scrutiny, which may lead to fewer treatments being approved by the FDA or other regulatory bodies, as well as more restrictive labeling of a product or a class of products for safety reasons, potentially including a boxed warning or additional limitations on the use of products, pharmacovigilance programs for approved products or requirement of risk management activities related to the promotion and sale of a product.

While we have completed two clinical trials for defibrotide to treat and prevent VOD, the data obtained from these trials may not be sufficient to obtain regulatory approval and we may be required to conduct additional clinical trials. We do not currently have the funds to run an additional clinical trial and we would likely need to obtain additional capital through equity or debt financings, loans and collaborative agreements with corporate partners, which may not be available to us on favorable terms, if at all. As a result, we may not be able to commercialize defibrotide for sale anywhere in the world. If we were unable to market and sell our product candidates, our business and results of operations would be materially and adversely affected and we may be unable to continue as a going concern.

The FDA and other regulatory authorities may require us to conduct other clinical trials of defibrotide to treat severe VOD or prevent VOD, which may delay or prevent approval and commercialization of our product candidate.

On December 7, 2009, final clinical trial results for our Phase III clinical trial of defibrotide to treat severe VOD and our Phase II/III pediatric prevention trial in Europe to prevent VOD were presented at the American Society of Hematology Conference in New Orleans. While data from these trials are encouraging, we may have to conduct a new clinical trial for defibrotide to treat VOD using a concurrent control group of untreated patients before obtaining regulatory approval in the U.S. or Europe for either the treatment or prevention indications. We currently do not, and we may never, have enough capital to commence and complete a new clinical trial of defibrotide to treat VOD. In addition, even if we are able to commence a new clinical trial, one or more clinical centers where the clinical trial is to be conducted may not be willing to conduct such a clinical trial on the basis that it is unethical to refuse treatment to patients when the treatment being investigated could potentially save their lives. The committee of clinical investigators who sponsored a Phase II/III clinical trial of defibrotide to treat VOD in Europe conducted by Consorzio Mario Negri Sud, which had a concurrent control group of untreated patients, cancelled the trial in October 2005 due to a lack of patient enrollment. We believe that patients were reluctant to enroll in the clinical trial due to the possibility of being placed into the control group and not receiving treatment. Therefore, we may never be able to obtain regulatory approval of defibrotide to treat VOD.

We may be required to suspend or discontinue any future clinical trials, if necessary, due to adverse events or other safety issues that could preclude approval of defibrotide and negatively affect our business model and stock price.

If we are required to conduct any future clinical trials for defibrotide, the trials may be suspended at any time for a number of safety-related reasons. For example, we may voluntarily suspend or terminate such clinical trials if, at any time, we believe that defibrotide presents an unacceptable risk to the clinical trial patients. In addition, institutional review boards or regulatory agencies may order the temporary or permanent discontinuation of our clinical trials at any time if they believe that the clinical trials are not being conducted in accordance with applicable regulatory requirements, including if they present an unacceptable safety risk to patients.

Administering any product candidate to humans may produce undesirable side effects. VOD is a condition associated with high dose chemotherapy and stem cell transplantation. Adverse events involving vascular disorders, coagulation and potentially life-threatening bleeding have been reported in VOD patients treated with defibrotide, which could potentially be related to the defibrotide therapy. Hypotension has been reported in patients participating in clinical trials of defibrotide to treat severe VOD, which may also be related to the drug. Also, we discontinued a 69-patient Phase I/II clinical trial of defibrotide to prevent deep vein thrombosis after hip surgery in Denmark in 2002, when three patients experienced hypotension after receiving the defibrotide intravenously. That trial was discontinued due to the hypotension and because defibrotide can also be administered orally to prevent deep vein thrombosis. These adverse events reports will be weighed by the FDA and other regulatory authorities in determining whether defibrotide will, from a risk-benefit perspective, be considered safe and effective to treat severe VOD, to prevent VOD, and to prevent deep vein thrombosis.

It is possible that new adverse events or safety issues will emerge from future data, which could impact conclusions relating to the safety of defibrotide. Any complications associated with the use of defibrotide would severely harm our business operations.

Product liability and other claims arising in connection with the testing our product candidates in human clinical trials may reduce demand for our products or result in substantial damages.

We face an inherent risk of product liability exposure related to defibrotide and the testing of defibrotide in human clinical trials and distribution through our named-patient and cost recovery programs. An individual may bring a

product liability claim against us if defibrotide causes, or merely appears to have caused, an injury.

These types of product liability claims may result in:

- decreased demand for defibrotide;
- injury to our reputation;
- withdrawal of clinical trial volunteers;
- related litigation costs; and
- substantial monetary awards to plaintiffs.

Although we currently maintain product liability insurance, we may not have sufficient insurance coverage, and we may not be able to obtain sufficient coverage at a reasonable cost. Our inability to obtain product liability insurance at an acceptable cost or to otherwise protect against potential product liability claims could prevent or inhibit the commercialization of any products that we or our collaborators develop, including defibrotide. If we are successfully sued for any injury caused by our products or processes, then our liability could exceed our product liability insurance coverage and our total assets.

Defibrotide could be subject to restrictions or withdrawal from the market and we may be subject to penalties if we fail to comply with regulatory requirements, if and when defibrotide is approved.

Any product for which we obtain marketing approval, together with the manufacturing processes, post-approval commitments, and advertising and promotional activities for such product, will be subject to continued regulation by the FDA and other regulatory agencies. Later discovery of previously unknown problems with defibrotide or its manufacture, or failure to comply with regulatory requirements, may result in:

- restrictions on defibrotide or manufacturing processes;
- withdrawal of defibrotide from the market;
- voluntary or mandatory recalls;
- fines;
- suspension of regulatory approvals;
- product seizures; or
- injunctions or the imposition of civil or criminal penalties.

If we are slow to adapt, or unable to adapt, to changes in existing regulatory requirements or adoption of new regulatory requirements or policies, we may lose marketing approval for defibrotide when and if defibrotide is approved.

Our manufacturing facility and the manufacturing facility of Patheon S.p.A., with whom we have contracted to fill and finish defibrotide, are subject to continuing regulation by Italian authorities and are subject to inspection and regulation by the FDA and EMA. These authorities could force us to stop manufacturing our products if they determine that we or Patheon are not complying with applicable regulations or require us to complete further costly alterations to our facilities.

We manufacture certain active pharmaceutical ingredients at our manufacturing facility in Italy. In addition, we have hired Patheon S.p.A. to process defibrotide into the finished drug at Patheon's manufacturing facility. These facilities are subject to continuing regulation by the Italian Health Authority and other Italian regulatory authorities with respect to manufacturing defibrotide. The facilities are also subject to inspection and regulation by the FDA and EMA with respect to manufacturing our product candidates for investigational use. Also, part of the process for obtaining approval from the FDA and EMA for defibrotide is approval by those authorities of these manufacturing facilities in compliance with current good manufacturing practices. After receiving initial approval, if any, the FDA or EMA will continue to inspect our manufacturing facilities, including inspecting them unannounced, to confirm whether we and Patheon are complying with good manufacturing practices.

These regulators may require us to stop manufacturing our products and may deny us approval to manufacture our product candidates if they determine that we or Patheon are not in compliance with applicable regulations. In addition, these regulators may require us to complete costly alterations to our facilities.

We use hazardous materials in our manufacturing facility, and any claims relating to the improper handling, storage, release or disposal of these materials could be time-consuming and expensive.

Our manufacturing of active pharmaceutical ingredients involves the controlled storage, use and disposal of chemicals and solvents. We are subject to laws and regulations governing the use, manufacture and storage and handling and disposal of materials and waste products. Although we believe that our safety procedures for handling and disposing of these hazardous materials comply with the standards prescribed by these laws and regulations, we cannot completely eliminate the risk of contamination or injury from hazardous materials. If an accident occurs, an injured party could seek to hold us liable for any damages that result and any liability could exceed the limits or fall outside the coverage of our insurance. We may not be able to maintain insurance on acceptable terms, or at all. We may incur significant costs to comply with current or future environmental laws and regulations.

We expect to rely upon a sole processor, Patheon S.p.A., to fill and finish defibrotide into marketable formulations, and we may not be able to quickly replace Patheon if it is unable to perform these services.

If Patheon does not or is not able to perform these services for any reason, it may take us time to find a replacement processor. Such a delay could potentially cause us to breach contractual obligations into which we may enter, violate local laws requiring us to deliver the product to those in need, and impact our revenues.

We may have difficulty obtaining raw material for defibrotide.

Defibrotide is based on pig intestines. If our current sources of pig intestines encounter safety or other issues that impact their ability to supply the pig intestines to us, as needed, we may not be able to find alternative suppliers in a timely fashion. In that case, we would have to slow or cease our manufacture of defibrotide.

If our third-party clinical trial vendors fail to comply with strict regulations, the clinical trials for defibrotide may be delayed or unsuccessful.

We do not have the personnel capacity to conduct or manage all of the clinical trials that may be necessary for the development of defibrotide. We have relied on third parties to assist us in managing, monitoring and conducting our clinical trials. In addition, we have entered into an agreement with MDS Pharma Services (U.S.) Inc. (now INC Research Inc.) to perform clinical research services in connection with clinical trials conducted in the United States and agreements with KKS-UKT, GmbH (now CenTrial, GmbH) and MDS Pharma Services S.p.A. (now Inc Research S.r.l.) to provide such services for our clinical trials in Europe. If these third parties fail to comply with applicable regulations or if they fail to adequately fulfill their obligations under the terms of our agreements with them, we may not be able to enter into alternative arrangements without undue delay or additional expenditures and, as a result, the clinical trials for defibrotide may be delayed or unsuccessful.

Furthermore, it is expected that the FDA will inspect some or all of the clinical sites participating in our clinical trials, or the sites of our third party vendors, to determine whether our clinical trials are being conducted in accordance with good clinical practice. If the FDA determines that our third-party vendors, or the sites themselves, are not in compliance with applicable regulations, we may be required to delay, repeat or terminate the clinical trials. Any delay, repetition or termination of our clinical trials could materially harm our business.

If we are unable to attract and retain qualified personnel and key relationships, we may be unable to successfully develop and commercialize defibrotide or otherwise manage our business effectively.

We are highly dependent on our senior management, whose services are critical to the successful implementation of research and development and manufacturing and regulatory strategies, and our ability to maintain relationships with qualified researchers. If we lose the services of one or more of the members of our senior management or other key researchers, our ability to successfully commercialize defibrotide or to otherwise manage our business effectively could be seriously harmed.

Replacing key employees may be difficult and may take an extended period of time because of the limited number of individuals in our industry with the breadth of specific skills and experience required to develop, gain regulatory approval of and commercialize defibrotide. Competition to hire from this limited pool is intense, and we may be unable to hire, train, retain or motivate these additional key personnel, if needed.

Moreover, we may need to hire additional personnel and add corporate functions that we currently do not have. To effectively manage our operations and growth, we will be required to continue to improve our operational, financial and management controls and reporting system and procedures, or to contract with third parties to provide these capabilities for us.

We are currently dependent on third parties to market and distribute defibrotide in finished dosage form, and we may continue to be dependent on third parties to market and distribute defibrotide.

Our internal ability to handle the marketing and distribution functions for defibrotide is limited. Our long-term strategy is to either develop marketing and distribution capacities internally or enter into alliances with third parties to

assist in the marketing and distribution of defibrotide. We have entered into an agreement with Sigma-Tau Pharmaceuticals, Inc. to market defibrotide to treat and prevent VOD in North America, Central America and South America and we may need to develop these capabilities internally or enter into similar agreements to market and distribute defibrotide to prevent VOD outside the Americas. We face, and will continue to face, intense competition with other companies over collaborative arrangements with pharmaceutical and biotechnology companies, relationships with academic and research institutions, attracting investigators and sites capable of conducting our clinical trials, and licenses of proprietary technology. Moreover, these arrangements are complex to negotiate and time-consuming to document. Our future profitability will depend in large part on our ability to enter into effective marketing agreements and our product revenues will depend on those marketers' efforts, which may not be successful.

All of our manufacturing capability is located in one facility that is vulnerable to natural disasters, telecommunication and information system failures, terrorism and similar problems, and we are not insured against losses that may be caused by any of these occurrences or events.

We conduct all of our manufacturing operations in a single facility located in Villa Guardia, near Como, Italy. This facility could be damaged by fire, flood, earthquake, power loss, telecommunication and information system failure, terrorism or a similar event. Our insurance covers damages to the facility, including the buildings, machinery, electronic equipment and goods, of up to approximately €15 million, but does not cover damages caused by any of the events listed above, including terrorism and some types of flooding. Although we believe that our insurance coverage is adequate for our current and proposed operations, there can be no guarantee that it will adequately compensate us for any losses that may occur. We are not insured against business interruption and we do not have a replacement manufacturing facility readily available.

We have sold Prociclide and Noravid (two formulations of defibrotide) in Italy to treat vascular disease with risk of thrombosis, which may affect the pricing of defibrotide in Europe for the prevention or treatment of VOD.

Until December 31, 2008, through a distribution agreement with Crinos S.p.A., we sold Prociclide and Noravid (both forms of defibrotide) in Italy to treat vascular disease with risk of thrombosis. While we have stopped selling Prociclide and Noravid for this treatment in Italy, if defibrotide is approved for sale in Europe to treat and/or prevent VOD , we may need to obtain regulatory approval of the price we charge for these uses of defibrotide. The regulators may impose an artificially low cap on defibrotide based on the relatively low price-point of Prociclide and Noravid previously sold in Italy for the treatment of vascular disease with risk of thrombosis.

Sirton, our affiliate, owes us a receivable that we may not be able to collect.

At December 31, 2010, Sirton owed us a receivable of €1.05 million and we owed Sirton a payable of €0.31 million. Sirton has been unable to make timely payments on the outstanding receivables. We may never be able to collect the net receivable due to us from Sirton.

In 2010, Sirton went into liquidation and, on June 28, 2010, Sirton was admitted by the Court of Como to a composition with creditors proceedings ("concordato preventivo") which was published on July 1, 2010. The composition with creditors was approved on February 3, 2011. At that time, a proposal for the acquisition of Sirton's assets was filed by a third party and approved by the Court of Como. A liquidator has been appointed, although a decision on the allocation of the proceeds from sale of Sirton's assets for distribution to the creditors has not yet been finalized. We understand that the liquidator may propose to satisfy the amounts due to secured creditors in full and pay the unsecured creditors a pro-rata share of 18.26% of the amounts due from the remaining assets.

We still rely upon Sirton Pharmaceuticals S.p.A. for various services, and we may not be able to quickly replace these services if it becomes bankrupt or otherwise unavailable.

Historically, FinSirton and Sirton provided us with a number of business services such as purchasing, logistics, quality assurance, quality control, analytical assistance for research and development, and regulatory services, as well as office space, personnel, administrative services, information technology systems and accounting services. Although we have substantially reduced the functions and activities provided by FinSirton and Sirton, we still depend on Sirton for certain infrastructure costs and quality control. These service agreements have recurring one-year terms that may be terminated by either party upon written notice to the other party at least one month prior to the expiration of the term. We are renegotiating those agreements with Sirton's new owner. If Sirton were to become bankrupt or otherwise cease providing these services, we may not be able to replace these services in a timely manner. Such a delay could impact revenue being generated from our compassionate use programs.

Our industry is highly competitive and subject to rapid technological changes. As a result, we may be unable to compete successfully or to develop innovative products, which could harm our business.

Our industry is highly competitive and subject to significant and rapid technological change as researchers learn more about diseases and develop new technologies and treatments. Incidence of VOD may decrease with new technologies and conditioning regimens, which will negatively impact our sales opportunities. While we are unaware of any other products or product candidates that treat or prevent VOD, we believe that other companies have products or are currently developing products to treat some of the same disorders and diseases that defibrotide is designed to treat. These companies include Genzyme Corp., Millennium Pharmaceuticals, Inc., Otsuka Pharmaceutical Co., Ltd., Eisai Co., Ltd., and Celgene Corp.

Many of these competitors have substantially greater research and development capabilities and experience, and greater manufacturing, marketing and financial resources than we have. In addition, these companies' products and product candidates are in more advanced stages of development than we are or have been approved for sale by the FDA and other regulatory agencies. As a result, these companies may be able to develop their product candidates and establish their product in the market before we can. Their products may also prove to be more effective, safer or less costly than defibrotide, which could hurt our ability to realize any significant revenues.

In May 2003, the FDA designated defibrotide as an orphan drug to treat severe VOD, and in January 2007, the FDA designated defibrotide as an orphan drug to prevent VOD. If the FDA approves the New Drug Applications for these uses of defibrotide that we intend to file, before approving a New Drug Application filed by anyone else, the orphan drug status will grant us limited market exclusivity for seven years from the date of the FDA's approval of our New Drug Application. However, a marketing authorization may be granted to another applicant for the same product if we give our consent to such authorization, we are unable to supply sufficient quantities of defibrotide, or if the second applicant can establish in its application that its product is safer, more effective or otherwise clinically superior to our product. In that case, our product would not have market exclusivity. There is no guarantee that the FDA will approve our New Drug Application before approving another company's product for these uses, although we are not aware of any other company researching defibrotide for these uses at this time. In such a case, however, the first product approved would have market exclusivity and our products would not be eligible for approval until that exclusivity period expires.

In July 2004, EMA designated defibrotide as an orphan medicinal product to both treat and prevent VOD. If the European regulators grant us a marketing authorization for those uses of defibrotide, we will have limited market exclusivity for those uses for ten years following the date of the approval. However, a marketing authorization may be granted to another applicant for the same product if we consent to such authorization, we are unable to supply sufficient quantities of defibrotide, or the second applicant can establish in its application that its product is safer, more effective or otherwise clinically superior to our product. In that case, our product would not have market exclusivity.

If we are unable to adequately protect our intellectual property, our ability to compete could be impaired.

Our long-term success largely depends on our ability to create and market competitive products and to protect those creations. Our pending patent applications, or those applications that we may file in the future, may not be granted. Until a patent is issued, the claims covered by the patent may be narrowed or removed entirely and, therefore, we may not obtain adequate patent protection. As a result, we may face unanticipated competition, or conclude that the risk of bringing products to the market is too great, thus adversely affecting our operating results.

Because of the extensive time required to develop, test and complete a regulatory review of a product candidate, it is possible that our relevant patent rights may expire before defibrotide can be approved for sale and commercialized, or within a short time after commercialization. We have been issued a patent in the U.S. and several other countries which covers the method for determining the biological activity of defibrotide. The patent expires in 2022 in most countries. This patent is important because the analytical release of a biological product like defibrotide is a key step in confirming the purity and biological activity of the final product. There may not be an opportunity to extend this patent and thereby extend exclusivity related to FDA and EMA, in which case we could face increased competition for defibrotide. Patent expiration could adversely affect our ability to protect future product development and, consequently, our operating results and financial position. In addition, generic innovators may be able to circumvent this patent and design a novel analytical method for determining the biological activity of defibrotide. In this case, a generic defibrotide could potentially be on the market once the relevant protections offered by our orphan designations end.

We also rely on trade secrets to protect our technology, particularly when we patent protection is inappropriate or unattainable. However, trade secrets are difficult to protect. While we use reasonable efforts to protect our trade secrets, our employees, consultants, contractors, outside scientific collaborators and other advisors may unintentionally or willfully disclose our information to competitors. To enforce a claim against a third party for illegally obtaining and using our trade secrets is expensive and time consuming, and the outcome is unpredictable. In addition, courts outside the United States are sometimes less willing to protect trade secrets. We intend to eventually license or sell our products in China, South Korea and other countries which do not have the same level of intellectual property rights and protections that exist in the United States and Europe. Moreover, our competitors may independently develop equivalent knowledge, methods and know-how.

Risks Related to Ownership of the American Depositary Shares

Our ADSs have generally had low trading volume, and its public trading price has been volatile.

The market price of our common stock has been highly volatile. Between our initial public offering on June 21, 2005 and December 31, 2010, the closing price of our American Depositary Shares, or ADSs, has fluctuated between $.33 and $24.40 per share, with an average daily trading volume for the twelve-month period ended December 31, 2010 of 109,864 ADSs. The market has experienced significant price and volume fluctuations for many reasons, some of which may be unrelated to our operating performance.

In addition to general market volatility, other factors that may have a significant adverse effect on the market price of our ADSs include:

- public announcements of decisions made by regulators in both the United States and abroad;
- public announcements of improvements, new commercial products, failures of products, or progress toward commercialization by our competitors or peers;
- influence of and control by our commercial partner and significant shareholder, Sigma-Tau Finanziaria S.p.A.;
- developments concerning proprietary rights, including patent and litigation matters;
- publicity regarding actual or potential results with respect to product candidates under development by us or by our competitors;

- regulatory developments; and
- quarterly fluctuation in our revenues and financial results.

We may not remain listed on the Nasdaq Global Market.

From the date of our public offering through May 2006, our ADSs were listed on the American Stock Exchange. Since May 2006, our ADSs have been listed on the Nasdaq Global Market. The Nasdaq Global Market sets forth various requirements that must be met in order for our ADSs to continue to be listed on the Nasdaq Global Market. We would be in violation of the continued listing requirements if:

- the closing bid price of our ADSs drops below $1.00 for a period of 30 consecutive trading days;
- our stockholders' equity falls below $10 million; or
- we fail to maintain a market value for publicly held securities of at least $5 million for 30 consecutive trading days.

In the event of any such violation, our ADSs could be delisted from the Nasdaq Global Market. The delisting of our ADSs could have negative results, including the potential loss of confidence by suppliers and employees, the loss of institutional investor interest, and fewer business development opportunities.

As of December 31, 2010, our stockholders' equity was $17.2 million (€12.9 million). If we fail to meet the stockholders' equity or fail to meet the minimum bid price and minimum market value requirements, we may be delisted from the Nasdaq Global Market.

Our largest shareholders exercise significant control over us, which may make it more difficult for you to elect or replace directors or management and approve or reject mergers and other important corporate events, including obtaining potential financing.

Our largest shareholder, FinSirton S.p.A., owned approximately 24% of our outstanding ordinary shares at December 31, 2010. Dr. Laura Ferro, our former Chief Executive Officer and President and a current member of our board of directors, together with members of her family, may be deemed to control FinSirton.

In addition, Sigma-Tau Finanziaria S.p.A., along with its affiliates, owned approximately 18% of our outstanding ordinary shares at December 31, 2010. Marco Codella, who is the Chief Financial Officer of Sigma-Tau Finanziaria, serves as a member of our board of directors. Moreover, we have licensed our rights in defibrotide to treat and prevent VOD to Sigma-Tau Pharmaceuticals, Inc., a wholly owned subsidiary of Sigma-Tau Finanziaria.

Both FinSirton and Sigma-Tau Finanziaria may substantially control the outcome of all matters requiring approval by our shareholders, including the election of directors and the approval of mergers or other important corporate events. They may exercise this ability in a manner that advances their best interests, and not necessarily your best interest. Also, the concentration of our beneficial ownership may have the effect of delaying, deterring or preventing a change in control, or may discourage bids for the ADSs or our ordinary shares at a premium over the market price of the ADSs. The significant concentration of share ownership may adversely affect the trading price of the ADSs due to investors' perception that conflicts of interest may exist or arise.

As discussed in our risk factor entitled "Our shareholders can prevent us from executing a financing by alleging that our board of directors acted with serious irregularities when approving such financing, because the terms of such financing could harm our company," each of FinSirton and Sigma-Tau Finanziaria own enough of our ordinary shares

to bring legal action against our board of directors and to possibly prevent us from completing an important corporate event, such as a financing. In addition, under Italian law, directors are not required to recuse themselves from participation in matters that present a conflict of interest. They are merely required to declare their conflict of interest. Accordingly, directors that are affiliated with our shareholders may be present for certain discussions that involve or impact the shareholders to which such directors are affiliated.

If a significant number of ADSs are sold into the market, the market price of the ADSs could significantly decline, even if our business is doing well.

Our outstanding ordinary shares, ordinary shares issuable upon exercise of warrants and ordinary shares issuable upon exercise of options are not subject to lock-up agreements. We have filed registration statements for the resale of most of our outstanding ordinary shares and related ADSs and all of our ordinary shares and related ADSs issuable upon exercise of our outstanding warrants and options. Such registration and ultimate sale of the securities in the markets may adversely affect the market for the ADSs.

You may not have the same voting rights as the holders of our ordinary shares and may not receive voting materials in time to be able to exercise your right to vote.

Except as described in this annual report and in the deposit agreement for the ADSs with our depositary, The Bank of New York Mellon, holders of the ADSs will not be able to exercise voting rights attaching to the ordinary shares evidenced by the ADSs on an individual basis. Holders of the ADSs will only have the right to instruct the depositary, as the holders' representative, to exercise these voting rights. You may not receive voting materials in time to instruct the depositary to vote, and it is possible that you, or persons who hold ADSs through brokers, dealers or other third parties, will not have the opportunity to exercise a right to vote.

You may not be able to participate in rights offerings and may experience dilution of your holdings as a result.

We may from time to time distribute rights to our shareholders, including rights to acquire our securities. Under our deposit agreement for the ADSs, the depositary will not offer those rights to ADS holders unless both the rights and the underlying securities to be distributed to ADS holders are either registered under the Securities Act of 1933, as amended, or exempt from registration under the Securities Act with respect to all holders of ADSs. We are under no obligation to file a registration statement with respect to any such rights or underlying securities or to endeavor to cause such a registration statement to be declared effective. In addition, we may not be able to take advantage of any exemptions from registration under the Securities Act. Accordingly, holders of our ADSs may be unable to participate in our rights offerings and may experience dilution in their holdings as a result.

You may be subject to limitations on transfer of your ADSs.

Your ADSs represented by the ADRs are transferable on the books of the depositary. However, the depositary may close its transfer books at any time or, from time to time when it deems expedient, in connection with the performance of its duties. In addition, the depositary may refuse to deliver, transfer or register transfers of ADSs generally when our books or the books of the depositary are closed, or if we or the depositary deem it advisable to do so under any requirement of law, any government or governmental body, any provision of the deposit agreement, or for any other reason.

Risks Relating to Being an Italian Corporation

The process of seeking to raise additional funds is cumbersome, subject to the verification of an Italian notary public in compliance with our bylaws and applicable law, and may require prior approval of our shareholders at an extraordinary shareholders' meeting.

We are incorporated under the laws of the Republic of Italy. The principal laws and regulations that apply to our operations, those of Italy and the European Union, are different from those of the United States. With some exceptions, in order to issue new equity or debt securities convertible into equity we must increase our authorized capital. In order to do so, our board of directors must meet and resolve to recommend that our shareholders approve an amendment to our bylaws increasing our capital. The holders of the majority of our outstanding shares must then approve that amendment at an extraordinary shareholders' meeting duly called. These meetings take time to call and it is very difficult to get a majority of the holders of all outstanding shares to vote in favor of the proposed resolution. In addition, an Italian notary public must verify that the capital increase is in compliance with our bylaws and with applicable Italian law. Further, under Italian law, our existing shareholders and any holders of convertible securities have preemptive rights (except in specific cases) to acquire any such shares pro-rated on their percentage interest in our company, and on the same terms as approved for such capital increase. Alternatively, our shareholders can delegate the power to increase our capital to the board of directors, but the board's right to exercise such power, if delegated, will expire after five years. If the board does not approve a capital increase by the end of those five years,

our board and shareholders would need to meet again to re-delegate this authority.

With respect to shareholders' resolutions approving a capital increase, Italian law provides that, in the event of the absence of minutes of the meeting, impossibility or illegality of the resolution, any interested person may, for a period of 180 days following the filing of the shareholders' resolution with the competent Register of Companies, challenge such resolution. If a shareholders' meeting was not called to approve the capital increase, the relevant resolution should be considered invalid and, any interested person may challenge the capital increase for a period of 90 days following the approval of the financial statements referring to the year during which the shareholders' resolution has been, also partially, executed. In addition, once our shareholders authorize a capital increase, all those authorized shares that have been subscribed need to be entirely paid-up before the shareholders may authorize a new capital increase. These restrictions could limit our ability to issue new equity or convertible debt securities on a timely basis.

Our shareholders can prevent us from executing a financing by alleging that our board of directors acted with serious irregularities when approving such financing, because the terms of such financing could harm our company.

On August 12, 2008, Sigma-Tau Finanziaria S.p.A., together with one of its affiliates, filed a claim in the Court of Como claiming that the members of our board of directors acted with serious irregularities, in violation of their duties as directors, in approving a potential financing because such financing was potentially harmful to the company. On August 18, 2008, the Court of Como issued a temporary order preventing us from moving forward with the potential financing. While this claim was later dismissed for lack of damages, the claim did, nonetheless, prevent the directors from implementing the financing. Any shareholder or group of shareholders constituting at least 10% of our outstanding ordinary shares could bring a similar action on a future board resolution regarding a financing or other important corporate action, and an Italian court could prevent the transaction from moving forward by issuing an order to that effect.

Italian law restricts the amount of debt securities that we may issue relative to our equity.

Under Italian law, we may issue debt securities in an amount not to exceed twice the sum of our capital, our legal reserve and any other disposable reserves appearing on our latest Italian GAAP balance sheet approved by our shareholders. The legal reserve is a reserve to which we allocate 5% of our Italian GAAP net income each year until it equals at least 20% of our capital. One of the other reserves that we maintain on our balance sheet is a "share premium reserve," meaning amounts paid for our ordinary shares in excess of the amount of such ordinary shares that is allocated to the capital. At December 31, 2010, the sum of our capital, our legal reserves and other reserves on our unaudited Italian GAAP balance sheet was € 31.7 million. If we issue debt securities in the future, until such debt securities are repaid in full, we may not voluntarily reduce our capital or allocate our reserves (such as by declaring dividends) if it results in the aggregate of the capital and reserves being less than half of the outstanding amount of the debt. If our equity is reduced by losses or otherwise such that the amount of the outstanding debt securities is more than twice the amount of our equity, some legal scholars are of the opinion that the ratio must be restored through a recapitalization of our company. If our equity is reduced, we could recapitalize by issuing new shares or having our shareholders contribute additional capital to us, although there can be no assurance that we would be able to find purchasers of new shares or that any of our current shareholders would be willing to contribute additional capital.

If we suffer losses that reduce our capital to less than €120 thousand, we would need to recapitalize, change our form of entity or be liquidated.

Italian law requires us to reduce our shareholders' equity and, in particular, our capital, to reflect on-going losses, in certain cases of losses exceeding 1/3 of the capital of the Company. We are also required to maintain a minimum capital of €120 thousand. At December 31, 2010, our unaudited Italian GAAP capital was approximately €14.9 million. If we suffer losses from operations that reduce our capital to less than €120 thousand, then we must either increase our capital (which we could do by issuing new shares or having our shareholders contribute additional capital to our company) to at least €120 thousand or convert the form of our company into an S.r.l., which has a lower capital requirement of €10 thousand. If we d not take these steps, our company could be liquidated.

We apply our operational losses against our legal reserves and capital. If our capital is reduced more than one-third as a result of losses, our board of directors must call a shareholders' meeting as soon as possible. The shareholders should take appropriate measures, which may include, inter alia, reducing the legal reserves and capital by the amount of the remaining losses, or carrying the losses forward for up to one year. If the shareholders vote to carry the losses forward up to one year, and the losses are still more than one-third of the amount of the capital at the end of the year, then we must reduce our capital by the amount of the losses.

Due to the differences between Italian and U.S. law, the depositary (acting as a shareholder on your behalf) may have fewer shareholder rights than you would have as a shareholder of a U.S. company.

We are incorporated under the laws of the Republic of Italy. As a result, the rights and obligations of our shareholders are governed by Italian law and our bylaws, and are in some ways different from those that apply to U.S. corporations. Some of these differences may result in the depositary (on your behalf) having fewer shareholder rights than you would have as a shareholder of a U.S. corporation. We have presented a detailed comparison of the Italian laws applicable to our company versus Delaware law in "Item 10, Additional Information, Comparison of Italian and Delaware Corporate Law." We compared the Italian laws applicable to our company against Delaware law because Delaware is the most common state of incorporation for U.S. public companies.

Italian labor laws could impair our flexibility to restructure our business.

In Italy, our employees are protected by various laws which afford them consultation rights with respect to specific matters regarding their employers' business and operations, including the downsizing or closure of facilities and employee terminations. In particular: (i) Law no. 604/1966, regulates the individual dismissals; (ii) Law no. 223/1991, concerns the collective dismissal procedure; (iii) Law no. 428/1990 as amended by legislative decree no. 18/2001, provides for the information and consultation procedure in case of transfer of the undertaking or part thereof and (iv) Legislative decree no. 25/2007, introduces a general right to information and consultation for employees. These laws and the collective bargaining agreements to which we are subject could impair our flexibility if we need to restructure our business.

FORWARD-LOOKING STATEMENTS

This annual report may contain forward-looking statements that involve substantial risks and uncertainties regarding future events or our future performance. When used in this annual report, the words "anticipate," "believe," "estimate," "may," "intent," "continue," "will," "plan," "intend," and "expect" and similar expressions identify forward-looking statements. should read statements that contain these words carefully because they discuss our future expectations, contain projections of our future results of operations or of our financial condition or state other "forward-looking" information. We believe that it is important to communicate our future expectations to our investors. Although we believe that our expectations reflected in any forward-looking statements are reasonable, these expectations may not be achieved. The factors listed in the section captioned "Risk Factors," as well as any cautionary language included in this annual report or incorporated by reference, provide examples of risks, uncertainties and events that may cause our actual results to differ materially from the expectations we describe in our forward-looking statements. Before you invest in our ordinary shares or ADSs, you should be aware that the occurrence of the events described in the "Risk Factors" section and elsewhere in this annual report could have a material adverse effect on our business, performance, operating results and financial condition. All subsequent written and oral forward-looking statements attributable to us or persons acting on our behalf are expressly qualified in their entirety by the cautionary statements set forth in this annual report. Except as required by federal securities laws, we are under no obligation to update any forward-looking statement, whether as a result of new information, future events, or otherwise.

You should rely only on the information contained in this annual report. We have not authorized anyone to provide you with information different from that contained in this annual report. The information contained in this annual report is accurate only as of the date of this annual report.

ITEM 4. INFORMATION ON THE COMPANY

HISTORY AND DEVELOPMENT OF THE COMPANY

We started as a group of pharmaceutical businesses founded in Italy in 1944 and have been involved in the research and development of drugs derived from DNA and DNA molecules since the 1970s. In 1993, we were formed by FinSirton S.p.A. as Pharma Research S.r.L., an Italian private limited company, for the purpose of pursuing research and development activities of prospective pharmaceutical specialty products. FinSirton is our largest shareholder, and may be deemed to be controlled by the Dr. Laura Ferro, our former Chief Executive Officer and President and currently one of our directors, and her family. In December 2000, Crinos Industria Farmacobiologica S.p.A., a subsidiary of FinSirton, contributed its plants, equipment and patents relating the development of biological pharmaceutical products, including all of its rights relating to defibrotide, to us in return for 98% of our ordinary shares. FinSirton continued to own the remaining 2% of our ordinary shares. At that time, we changed from a private limited company to a corporation and in July 2001 we changed our name to Gentium S.p.A. Under our current bylaws, the duration of our company will expire on December 31, 2050. We are governed by the Italian Civil Code.

In May 2002, Crinos Industria Farmacobiologica S.p.A. sold its commercial division, including its products, licenses and patents relating to pharmaceutical products in Italy, including the brand name "Crinos," to a newly formed subsidiary, called Crinos S.p.A., of Stada, a leader in the generic pharmaceutical industry in Europe. At that time, Crinos Industria Farmacobiologica S.p.A. changed its name to Sirton Pharmaceuticals S.p.A. In 2003 and 2004, Sirton distributed its 98% ownership interest in our ordinary shares to FinSirton as dividends. As a result, FinSirton became our sole shareholder, owning 100% of our ordinary shares at that time. In January 2005 and April 2005, FinSirton sold a portion of its ownership interest to third parties. In June 2005, we conducted an initial public offering of 2,400,000 ADSs, each representing the right to receive one ordinary share, and listed the ADSs on the American Stock Exchange. FinSirton remains our largest shareholder, owning approximately 24% of our outstanding ordinary shares at December 31, 2010. FinSirton also holds 100% of the outstanding shares of Sirton.

Our principal executive offices are located at Piazza XX Settembre 2, 22079 Villa Guardia (Como), Italy. Our telephone number is +39 031 385111. Our website is located at www.gentium.it. The information contained on our website is not part of this annual report. Our registered agent for service of process is CT Corporation System, located at 111 Eighth Avenue, 13th Floor, New York, New York 10011, telephone number (212) 894-8940.

We have Italian, United States and international trademark rights in “Gentium,” United States and European Union trademarks in “Gentide,” international and Italian trademark rights in “Oligotide” and Italian trademark rights in “Pharma Research” and “Dinelasi.” We also have a number of patent registrations issued and pending in Italy, the United States and other countries. This annual report also refers to brand names, trademarks, service marks, and trade names of other companies and organizations, and these brand names, trademarks, service marks, and trade names are the property of their respective holders.

This annual report contains market data and industry forcasts that were obtained from industry publications and third parties.

CAPITAL EXPENDITURES

The following table sets forth our capital expenditures for each year in the three-year period ended December 31, 2010.

	For the Year Ended December 31,		
(in thousands)	2008	2009	2010
Land and buildings	€ 4	€ -	€ -
Plant and machinery	544	206	129
Industrial equipment	179	5	7
Other	13	23	9
Leasehold improvements	27	3	50
Computer Software	224	12	-
Construction in progress	172	28	10
Total	€ 1,163	€ 277	€ 205

All of these capital expenditures are in Italy. We are financing these expenditures through existing revenue, licensing fees, offerings of our ordinary shares and loans from third parties.

BUSINESS OVERVIEW

We are building upon our experience with defibrotide, an investigational drug based on a mixture of single-stranded and double-stranded DNA extracted from pig intestines and purified to a set of defined molecular weights and charges which our founding company discovered over 20 years ago. We are focused on the development and manufacture of defibrotide to treat and prevent VOD, a condition that occurs when veins in the liver are blocked as a result of cancer treatments, such as chemotherapy or radiation, that are administered prior to stem cell transplantation. Severe VOD is the most extreme form of VOD and is linked to multiple-organ failure and high rates of morbidity and mortality. We have concluded a Phase III clinical trial of defibrotide to treat severe VOD in the United States, Canada and Israel, and a Phase II/III clinical trial of defibrotide in Europe to prevent VOD in children. While we have not yet obtained regulatory approval to market defibrotide, we are authorized to distribute defibrotide on a pre-approval basis under a treatment IND protocol in the U.S. and through a named-patient program throughout the rest of the world.

Due to the historically low complete response and survival rates and lack of treatments for VOD, we believe there is an immediate need for a drug that treats and prevents VOD. The FDA has a “fast track” designation program which is designed to facilitate the development and expedite the review of new drugs that are intended to treat serious or life-threatening conditions and that demonstrate the potential to address unmet medical needs. The FDA has designated defibrotide to treat severe VOD as a fast track product. FDA approval of defibrotide for these uses remains dependent upon the sufficiency of data collected from our clinical trials.

On December 7, 2009, we announced final clinical trial results for our current Phase III clinical trial of defibrotide to treat severe VOD and our Phase II/III pediatric prevention trial in Europe to prevent VOD. On December 7, 2010 we announced interim clinical trial results with defibrotide in the treatment of severe VOD with multi-organ failure from the on-going treatment IND expanded access program. We have recently completed certain preclinical and clinical studies requested by regulatory authorities. As part of our overall strategy, we anticipate filing for regulatory approval for defibrotide in the U.S. and Europe by the end of second quarter 2011. We expect to utilize the data from the two studies, together with data obtained from our compassionate use programs, through which we have been authorized to distribute defibrotide on a pre-approval basis, to support our regulatory submissions and any future clinical trials that may be necessary. We are also working on our U.S. regulatory strategy with our commercial partner, Sigma-Tau Finanziaria S.p.A. and its affiliate Sigma-Tau Pharmaceuticals, Inc., to which we have licensed our commercial rights to defibrotide for both the treatment and prevention of VOD in the Americas. We are currently establishing our sales force, as we intend to commercialize defibrotide in the major European countries on our own.

We manufacture defibrotide and sulglicotide at our manufacturing facility near Como, Italy, and we lease a facility from one of our affiliates, Sirton, to manufacture urokinase. These products are active pharmaceutical ingredients used to make other drugs. Our revenues from the sales of these products to date have totaled €3.72 million, €4.80 million and €6.53 million in 2008, 2009 and 2010, respectively. In 2009, we launched a named-patient program and cost recovery program, which have generated approximately €4.90 million and €13.18 million in net sales for the years ended December 31, 2009 and 2010, respectively.

Our strategy is to obtain regulatory approval for defibrotide to treat and prevent VOD. Since 2004, we have spent more than €10 million on upgrades to our facilities, which we believe will facilitate the FDA and European regulatory approval of defibrotide and enable our future production of defibrotide. We plan to work with our existing license partner, Sigma-Tau Pharmaceuticals, Inc., to develop and commercialize defibrotide, and are seeking additional license partners to help with the development and commercialization of defibrotide.

Market Overview

Chemotherapy, radiation therapy and hormone therapy treatments are used to target and kill cancer cells. In some cases, the therapy treats the cancer directly; in other cases, it is administered to prepare the patient for a stem cell or bone marrow transplant, which then treats cancer or other diseases. Unfortunately, these therapies often have significant negative side effects, including damage to the cells that line the blood vessel walls. The damage to these cells can lead to various disorders of the vascular system. Some patients may not be able to continue with cancer treatments because they develop these vascular system complications; other patients who are considered to be at high risk of developing these vascular system complications may not receive optimal cancer treatments or any treatment at all.

One disorder of the vascular system that can result from chemotherapy, radiation therapy, hormone therapy or stem cell and bone marrow transplants is VOD. These therapies can cause extensive damage to the cells that line the walls of small veins in the liver. The body's natural response is to swell or clot the sites of injury, but the cell damage blocks or "occludes" the vein. This blockage of the veins is called "Hepatic Veno-Occlusive Disease," or VOD. VOD can cause damage to the liver and, in its severe form, leads to failure of the liver and other organs (multiple-organ failure), which usually results in death. According to 2003 data collected from the International Bone Marrow Transplant Registry and the European Bone Marrow Transplant Registry, approximately 21,000 people receive a bone marrow transplant, which is a type of stem cell transplant, each year in the United States. Based on our review of more than 200 articles in medical literature, we believe that approximately 12% of patients who undergo a stem cell transplant develop VOD. According to an article in the November 15, 1998 edition of Blood, the Journal of the American Society of Hematology, by Enric Carreras et. al., approximately 28% of patients who develop VOD progress to severe VOD. A historical study conducted by Dana-Farber at three centers consisting of 38 patients showed that only approximately 11% of patients who develop severe VOD achieve a complete response within 100 days after stem cell transplantation and only approximately 20% survive for more than 100 days. VOD poses a severe risk to the victim's health and life. To our knowledge, there is no FDA or EMA approved treatments for VOD at this time.

Strategy

Our strategic objective is to obtain regulatory approval for defibrotide to treat and prevent VOD. We plan to continue to work with our existing license partner, Sigma-Tau Pharmaceuticals, Inc., to commercialize defibrotide in the Americas. Outside of the Americas, we are seeking additional license partners to help with the development and commercialization of defibrotide. We are also attempting to grow our active pharmaceutical ingredient, or API, business through increased sales of sulglicotide and urokinase.

- Obtain regulatory approval to use defibrotide to treat and prevent VOD. Gentium, as well as independent investigators, have conducted several studies that show the potential efficacy and safety of defibrotide as a treatment and a method of prevention of VOD (see detail under "Product Candidate" section below). Defibrotide has received orphan status from both the FDA and EMA. In addition, we have received fast track designation for the use of defibrotide for the treatment of severe VOD prior to stem cell transplantation. The approval of defibrotide for either the treatment or prevention of VOD may be dependent on one or more future clinical trials. It is possible that both the FDA and EMA will view the results of treatment and prevention trials as supportive of one another, although the regulatory approval, if awarded, may limit the use of defibrotide to prevention or treatment only.

- Increase our marketing capacity, including the use of strategic partnerships. We have a strategic license agreement with Sigma-Tau Pharmaceuticals, Inc., under which we will work collaboratively to market defibrotide to treat and prevent VOD in North America, Central America and South America once regulatory approval is obtained. Pursuant to the license agreement, Sigma-Tau Pharmaceuticals, Inc. will have a right of first refusal in those territories with respect to offers made by third parties to market defibrotide to prevent VOD. We intend to develop the

capacity to market defibrotide in other jurisdictions and/or pursue similar agreements with other strategic partners to market defibrotide in Europe and the Asia Pacific.

- Compassionate use programs to maximize pre-approval data. We distribute defibrotide on a pre-approval compassionate use basis through our named-patient and treatment IND programs. We obtain data on the efficacy and safety of defibrotide through these programs. We expect to utilize this data to supplement the data obtained from our completed clinical trials and any future clinical trials that may be conducted as necessary. As of February 28, 2011, approximately 800 patients have received defibrotide through these programs.

- Growth of API Business. We currently sell sulglicotide to Samil for use in the South Korean market and to Crinos for use in the Italian market. We also sell urokinase to Crinos for use in the Italian market and to UCB for use in the Spanish market. Our goal is to maximize the utilization of our manufacturing facility and we are exploring ways to increase our capacity to sell urokinase and sulglicotide. We are also looking at re-negotiating our existing supply agreements to achieve greater profitability and longer-term commitments.

Product Candidate

Defibrotide is an investigational drug based on a mixture of single-stranded and double-stranded DNA extracted from pig intestines and purified to a set of defined molecular weights and charges, which is under development for the treatment and prevention of VOD, a disease caused by certain cancer treatments, such as chemotherapy and radiation that are administered prior to stem cell transplantation. Currently, and to the best of our knowledge, there is no FDA or EMA approved treatments for this life-threatening disease. The FDA granted orphan status to defibrotide as a treatment for severe VOD in 2003, and as a method of prevention of VOD in 2007. EMA granted a similar status to defibrotide as a VOD treatment and preventative measure in 2004. Orphan status provides us with limited market exclusivity upon regulatory approval. The FDA has also granted fast-track product designation to defibrotide for the treatment of VOD. While we have not yet obtained regulatory approval to market defibrotide, we are authorized to distribute defibrotide on a pre-approval basis under a treatment IND protocol in the U.S. and through a named-patient program throughout the rest of the world.

Defibrotide to treat severe VOD

The December 2000 edition of the British Journal of Hematology published the results of a 40 patient “compassionate use” study on defibrotide to treat VOD, which was conducted in 19 centers in Europe from December 1997 to June 1999. Twenty-two patients, or 55%, showed a complete response to the treatment. Nineteen patients, or 47%, survived more than 100 days after stem cell transplantation. The study found that four of the 19 patients who survived for more than 100 days subsequently died. Twenty-eight patients were deemed likely to die or exhibited multiple-organ failure. Ten of the 28 “poor risk” patients, or 36%, showed a complete response within 100 days after stem cell transplantation, all of whom survived for at least 100 days. The study concluded that defibrotide was generally safely administered with no significant side-effects.

The December 15, 2002 edition of Blood published results of a study involving 88 patients with severe VOD following stem cell transplants that were treated with defibrotide from March 1995 to May 2001. 19 patients were treated under individual Investigational New Drug Applications and 69 patients were part of a multi-center Phase I/II clinical trial conducted under an Investigational New Drug Application submitted by a Dana-Farber investigator. The primary goal of the trial was to assess the potential effectiveness of the drug and its side effects, if any. All patients in the clinical trial received defibrotide on an emergency basis. This study found that 32 patients, or 36%, showed a complete response within 100 days after stem cell transplantation, and 31 patients, or 35%, survived for at least 100 days after stem cell transplantation with only minimal adverse effects, the primary effect being transient mild hypotension. Thirteen of those 31 patients who had survived more than 100 days died by October 2001, the last date on which survival information was available. No mortality from VOD or other toxicity related to the cancer treatment was observed beyond 134 days after treatment with defibrotide, with the most common cause of later death being relapse.

The Dana-Farber investigator also sponsored a Phase II clinical trial in the United States under his Investigational New Drug Application, involving 150 stem cell transplant patients with severe VOD, 141 of whom were evaluable, at nine cancer centers. This trial was partially funded by a $525 thousand grant from the orphan drug division of the FDA. The purpose of this trial was to evaluate the effectiveness of defibrotide, including its effect on the survival rate of patients with severe VOD, the effectiveness of the dosages administered and potential adverse side effects. The primary endpoint was complete response, with survival after 100 days as a secondary endpoint. The Dana-Farber investigator presented the results from this Phase II clinical trial at the 47th Annual Meeting of the American Society of Hematology on December 12, 2005. The results showed that of 141 patients evaluable for response, 65 patients, or 46%, showed a complete response within 100 days after stem cell transplantation and 62 patients, or 41%, survived for at least 100 days after stem cell transplantation, with minimal adverse effects.

The January 2004 edition of Bone Marrow Transplantation published the results of a study involving 45 children and adolescents who contracted VOD following stem cell transplants and were treated with defibrotide. Twenty-two of the 45 patients had severe VOD. Thirty-four of the 45 patients, or 76%, had a complete response within 100 days after stem cell transplantation and 29 patients, or 64%, survived for at least 100 days after stem cell transplantation. Of the 22 patients with severe VOD, 11 patients, or 50%, had a complete response and 8 patients, or 36%, survived for at least 100 days after stem cell transplantation. The study showed that defibrotide was well tolerated; about one-third of the patients developed a form of coagulopathy, and treatment was discontinued in two cases where a severe bleeding disorder was observed, although the events could not be clearly attributed to defibrotide.

We initiated a historically controlled Phase III clinical trial in the United States, Canada and Israel for this use in December 2005 in patients with severe VOD. The primary endpoint is complete response within 100 days after stem cell transplantation and the secondary endpoint is survival after 100 days.

On December 7, 2009, final clinical trial results for our current Phase III clinical trial of defibrotide to treat severe VOD were presented at the American Society of Hematology Conference in New Orleans. On an intent to treat basis (ITT), 24% of patients in the defibrotide arm compared to 9% of patients in the historical control arm achieved complete response at 100 days (p=0.0148). For the secondary efficacy analysis on an ITT basis, the mortality rate at day 100 was 75% for patients in the historical control arm compared to 62% for patients in the defibrotide arm (p=0.0508). The ITT analysis included 123 patients with symptoms consistent with VOD that were identified and then reviewed for eligibility in the historical control arm by an independent medical review committee. 32 of the patients were unequivocally diagnosed with severe VOD and multi-organ failure (graft versus host disease was ruled out) and met all protocol-required entry criteria. 102 patients were enrolled in the defibrotide treatment group and baseline characteristics were balanced between the two arms.

On December 7, 2010, interim results of a Treatment IND Study of defibrotide in the treatment of severe VOD were presented at the American Society of Hematology Conference in Orlando. This study is currently ongoing in the US. The interim analysis reported results of 104 patients with severe VOD. Patients were enrolled at 36 US institutions between December 2007 and September 2009, 31 patients (30%) achieved a complete response (CR) by D+100, 33 patients (32%) survived to Day + 100 post stem cell transplant. In this population, no unexpected toxicities were observed and defibrotide-associated toxicities were consistent with prior studies. A poster on the safety of defibrotide was also presented. At time of the presentation, 1824 stem cell transplant patients have received defibrotide in controlled and uncontrolled studies for the treatment or prevention of VOD/sVOD; the majority of these patients received the current 25 mg/kg/day dose. A review of safety for defibrotide was undertaken to assess the overall safety profile of defibrotide in this more compromised stem cell transplantation population, predisposed to increased regimen related toxicities, including hemorrhagic and thrombotic complications. The safety database of 1824 includes data from the Phase II and the Phase III sVOD treatment studies and the phase Phase II/III pediatric prevention of VOD study. Overall, the incidence of related adverse events was 1% (9 out of 772 patients) in VOD prophylaxis and 9% (96 out of 1052 patients) in patients who had received defibrotide for the treatment of VOD/sVOD. Defibrotide was well-tolerated, with adverse events (including hemorrhages) reported with similar frequency to the control.

Defibrotide to prevent VOD

We believe there is a significant opportunity to market defibrotide to patients at risk of developing VOD. Based on our research of VOD, we believe that recipients of high doses of chemotherapy, radiation therapy or hormone therapy or of therapies that prepare for stem cell transplants have an elevated risk of developing VOD. The European Group for Blood and Marrow Transplantation, a not-for-profit scientific society, conducted a Phase II/III clinical trial in Europe and Israel involving defibrotide to prevent VOD in children. Unlike our Phase III treatment trial in the United States, this clinical trial included a randomized control group of patients who received no treatment unless they developed VOD, at which time they received defibrotide treatment.

The results of a study on defibrotide involving patients at high risk of VOD were presented at the 2002 annual meeting of the American Society of Hematology. One of 57 patients who received defibrotide as a preventative agent developed VOD. No patients who received the drug experienced significant bleeding.

At the 2005 annual meeting of the European Group for Blood and Marrow Transplantation, the results of a study on defibrotide administered to patients who received chemotherapy and stem cell transplants were announced. Eight of 44 patients, or 18%, who received defibrotide developed VOD, three of which patients, or 7%, developed severe VOD. By comparison, four of 16 control group patients, or 25%, who received heparin instead of defibrotide developed VOD, two of which, or 12.5%, developed severe VOD. There were no serious adverse events attributed to the use of defibrotide.

At the 2006 annual meeting of the American Society of Hematology conference, the results from a preliminary pilot clinical study in Switzerland by the University Hospital of Geneva on defibrotide in patients at high risk of VOD were announced. The results suggest that defibrotide may effectively and safely prevent VOD. The study tested patients who received stem cell transplants. None of the 157 successive transplant patients who received defibrotide as a preventative agent developed VOD. By comparison, prior to the study, 10 of 52 patients who underwent transplants in the same center developed VOD, which was fatal in three cases. The study report indicated that mild to moderate toxicity, including mild nausea, fever and abdominal cramps, was observed in patients who received defibrotide, although it was difficult to determine whether the toxicity was directly attributable to the defibrotide, the chemotherapy that preceded the stem cell transplants or other drugs used during the stem cell transplants. The study report did not indicate the number of patients who experienced this toxicity.

The July 2007 edition of Bone Marrow Transplant published the results of a study on defibrotide administered to patients who received stem cell transplants. While a majority of these patients were recipients of reduced intensity cancer treatments, there were other factors exposing each of them at risk for VOD. None of the 58 patients who received defibrotide as a preventative agent developed VOD. No serious adverse events were reported.

The results of a study on defibrotide in patients who received stem cell transplants and had elevated risks for VOD were reported in the November 16, 2007 edition of Blood. One of 41 evaluable patients who received defibrotide as a preventative agent developed VOD. No serious adverse events were reported.

On December 7, 2009, final clinical trial results from our Phase II/III pediatric prevention study to prevent VOD were presented at the American Society of Hematology conference. Defibrotide demonstrated a 40% reduction in the incidence of VOD within 30 days after stem cell transplantation. The analysis included 356 patients; 180 patients in the prophylaxis arm and 176 patients in the control arm. Although the study was not powered to assess mortality, a composite score was measured as a secondary endpoint, incorporating VOD-associated morbidity (including respiratory failure, renal failure, encephalopathy) and mortality; this score significantly favored defibrotide prophylaxis (p=0.0340). The study confirmed that the mortality in patients with VOD, independent of severity, is four times higher than in patients without VOD. Additionally, the incidence and severity of acute graft versus host disease (GvHD) by day 100 in the allogeneic SCT recipients (246 patients) was significantly reduced from 63% for the control arm to 45% for the prophylaxis arm (p=0.0044 for incidence of GvHD and p=0.0032 for severity). Defibrotide was well tolerated and no difference in adverse events was observed between the two study arms.

Defibrotide Pre-Approval

Historically, we sold defibrotide as an active pharmaceutical ingredient to our affiliate, Sirton, who then used the active pharmaceutical ingredient for defibrotide to fill and finish the product into ampoule and capsule forms. Sirton then sold these forms of defibrotide to Crinos S.p.A., a subsidiary of Stada Arzneimittel AG. Crinos, pursuant to a distribution agreement entered into with us, sold these products throughout Italy, under the trademarks Prociclide and Noravid, to treat and prevent vascular disease with risk of thrombosis.

In 2007, our relationship with Sirton changed from a customer to a contract manufacturer relationship, and we sold the finished forms of Prociclide and Noravid to Crinos directly. On December 31, 2008, the distribution agreement with Crinos expired and, keeping consistent with our overall strategy, we elected not to renew this agreement and discontinued the manufacture of defibrotide to be finished into Prociclide and Noravid. We did not pursue any sales of Prociclide and Noravid in the Italian market in 2009. On August 19, 2009, the Italian Health Agency accepted our request to withdraw the marketing authorization for Prociclide and Noravid; however, these products were sold in Italy until May 2010. Subsequently, the marketing authorization was terminated. We made the request to withdraw the marketing authorization of these forms of defibrotide as part of our overall strategy regarding the development of defibrotide to treat and prevent VOD.

On March 6, 2009, we entered into a supply and distribution agreement with IDIS Limited, whereby IDIS contracted to be the exclusive supplier of defibrotide on a named-patient supply basis in all countries other than countries in Europe and the Americas. This agreement was amended on April 15, 2009 to include all countries other than Italy and countries in the Americas, amended on May 22, 2009 to include all countries other than Italy and the United States of America, and further amended on September 23, 2010 to include all countries other than Italy, South Korea and the United States of America. We supply the finished and labeled product to IDIS who, in turn, provides the product directly to hospitals in all countries except Italy, South Korea and the United States of America.

We have also instituted an expanded access program, which gives patients diagnosed with VOD in the United States access to defibrotide under a treatment IND. Under an expanded access program, the FDA allows early access to investigational drugs that are being developed to treat serious or life-threatening diseases for which there is no satisfactory alternative therapy. We decided to undertake this expanded access program due to the large number of requests for compassionate use of defibrotide, and the corresponding burden that sites and investigators have endured to obtain institutional review board and FDA approval for such compassionate use requests. On September 29, 2009, we entered into an agreement with US Oncology Clinical Development, whereby US Oncology was contracted as a clinical research organization to administer and recover costs on our behalf in connection with this program. We expect to collect additional usage tolerability and safety data from patients of this program to support our planned New Drug Application for the treatment of Severe VOD and/or the prevention of VOD.

Our revenues from sales of defibrotide, including Prociclide and Noravid, were €1.73 million, €4.90 million, and €13.18 million for 2008, 2009 and 2010, respectively.

Other Products

Sulglicotide

Sulglicotide is developed from swine duodenum and appears to have ulcer healing and gastrointestinal protective properties. We sell sulglicotide primarily to Samil, a South Korean company, for its use in manufacturing a product in South Korea, and to Crinos S.p.A for its distribution in the Italian market.

Urokinase

Urokinase is made from human urine and has the potential to dissolve fibrin clots and. This product is used to treat various vascular disorders such as deep vein thrombosis and pulmonary embolisms. We sell urokinase to a number of companies, including Crinos and UCB.

Seasonality

Seasonality does not affect our business, although the timing of manufacturer orders can cause variability in sales.

Regulatory Matters

Overview

The preclinical and clinical testing, manufacture, labeling, storage, distribution, promotion, sale, import and export, reporting and record-keeping of our product candidates are subject to extensive regulation by governmental authorities in the United States, principally the FDA and corresponding state agencies, and regulatory agencies in foreign countries.

Non-compliance with applicable regulatory requirements can result in, among other things, injunctions, seizure of products, total or partial suspension of product manufacturing and marketing, failure of the government to grant approval, withdrawal of marketing approvals, civil penalty actions and criminal prosecution. Except as discussed below, we believe that we are in substantial compliance in all material respects with each of the currently applicable laws, rules and regulations mentioned in this section. During the most recent biannual inspection of our manufacturing facility by the Italian Health Authority in February 2007, the Italian Health Authority noted by way of observations certain deficiencies in regard to the operation of our facility. We have corrected all of the deficiencies. Also, a regional Italian regulatory inspector, during an April 2005 inspection of our manufacturing facility, requested that we install an exhaust vent on one of our machines. We have installed this device. In order to obtain FDA approval for the sale of any of our product candidates, the FDA must determine that this facility meets their current good manufacturing practices, or GMP, including requirements for equipment verification and validation of our manufacturing and cleaning processes. The FDA has not yet inspected our facility, but since 2004 we have spent over €10 million in upgrades to our facility in anticipation of such an inspection. We are not aware of any other situation that could be characterized as an incidence of non-compliance in the last three years.

United States Regulatory Approval

FDA regulations require us to undertake a long and rigorous process before any of our product candidates may be marketed or sold in the United States. This regulatory process typically includes the following general steps:

- our performance of satisfactory preclinical laboratory and animal studies under the FDA's good laboratory practices regulations;
- our submission to and acceptance by the FDA of an IND which must become effective before human clinical trials may begin in the United States;
- our successful completion of a series of adequate and well-controlled human clinical trials to establish the safety, purity, potency and effectiveness of any product candidate for its intended use under the FDA's good clinical practices regulations;
- our submission to, and review and approval by, the FDA of a marketing application prior to any commercial sale or shipment of a product; and
- our development and demonstration of manufacturing processes which conform to FDA-mandated current good manufacturing practices.

This process requires a substantial amount of time and financial resources. In 2002, the FDA announced a reorganization that resulted in the shift of the oversight and approval process for certain therapeutic biologic drugs and the related staff from the Center for Biologics Evaluation and Research to the Center for Drug Evaluation and Research. Our initial product candidate, defibrotide to treat severe VOD, is being regulated through the latter.

Preclinical Testing

Preclinical tests generally include laboratory evaluation of a product candidate, its chemistry, formulation, stability and toxicity, as well as certain animal studies to assess its potential safety and effectiveness. We must submit the results of these preclinical tests, together with manufacturing information, analytical data and the clinical trial protocol, to the FDA as part of an Investigational New Drug Application, which must become effective before we may begin any human clinical trials. An application automatically becomes effective 30 days after receipt by the FDA, unless, prior to the expiration of this 30-day time period, the FDA raises concerns or questions about the intended conduct of the trials and imposes what is referred to as a clinical hold. If one or more of our products is placed on clinical hold, we would be required to resolve any outstanding issues to the satisfaction of the FDA before we could begin clinical trials. Preclinical studies generally take several years to complete, and there is no guarantee that an Investigational New Drug Application based on those studies will become effective, allowing clinical testing to begin.

Clinical Trials

In addition to FDA review of an Investigational New Drug Application, each clinical institution that desires to participate in a proposed clinical trial must obtain approval of its clinical protocol by an Institutional Review Board. The Institutional Review Boards consider, among other things, ethical factors, informed consent and the selection and safety of human subjects. Clinical trials must also be conducted in accordance with the FDA's good clinical practices requirements. The FDA, and/or the Institutional Review Board associated with the institution at which a clinical trial is being performed, may order the temporary or permanent discontinuation of a clinical trial if, at any time, it believes that the clinical trial is not being conducted in accordance with FDA requirements or presents an unacceptable risk to the clinical trial patients.

Human clinical trials are typically conducted in three sequential phases, which may overlap, and include the following:

Phase I

In Phase I clinical trials, a product candidate is typically administered either to healthy people or to patients with the medical condition for which the new drug is intended to be used. The main purpose of the trial is to assess a product candidate's safety and the ability of the human body to tolerate the product candidate. The trial may also be conducted to assess the dosage, absorption, distribution, excretion and metabolism of the product candidate.

Phase II

During Phase II, a product candidate is given to a limited number of patients with the disease or medical condition for which it is intended to be used in order to:

- further identify any possible adverse side effects and safety risks;
- assess the preliminary or potential effectiveness of the product candidate for the specific targeted disease or medical condition; and
- assess dosage tolerance and determine the optimal dose for a Phase III trial.

Phase III

If and when one or more Phase II trials demonstrate that a specific dose or range of doses of a product candidate is likely to be effective and has an acceptable safety profile, then one or more Phase III trials are generally undertaken to demonstrate clinical effectiveness and to further test for safety in an expanded patient population, with the goal of evaluating the product's efficacy and the overall risk-benefit relationship of the product candidate. The successful demonstration of clinical effectiveness and safety in one or more Phase III trials is generally a prerequisite to the filing of an application for FDA approval of the product candidate.

After approval, the FDA may also require a Phase IV clinical trial to continue to monitor the safety and effectiveness of the product candidate.

The sponsor must submit to the FDA the results of the pre-clinical and clinical trials, together with, among other things, detailed information on the manufacturing and composition of the product, in the form of a New Drug Application or Biologics License Application. Once the submission has been accepted for filing, the FDA has 180 days to review the application and respond to the applicant. The review process is often extended significantly as

a result of FDA requests for additional information or clarification.

Post-Approval Regulations

Any approval of a product candidate is limited to specific clinical uses. Subsequent discovery of previously unknown problems relating to a product may result in additional restrictions on its use or even complete withdrawal of the product from the market. All FDA-approved products that we manufacture or distribute are subject to continuing regulation by the FDA, which requires record-keeping and reporting of adverse events or experiences. Drug manufacturers and their subcontractors are required to register their establishments with the FDA and state agencies, and are subject to periodic inspections by the FDA and state agencies to ensure compliance with current good manufacturing practices, or GMPs, which impose rigorous procedural and documentation requirements upon us and our contract manufacturers. Failure to comply with these requirements may result in, among other things, total or partial suspension of production activities, a denial by the FDA of marketing approvals, or withdrawal, suspension, or revocation of marketing approvals.

If the FDA approves one or more of our product candidates, we, along with our contract manufacturers, must provide certain safety and effectiveness information while the drug is being marketed. Changes in the product, as well as changes in the manufacturing process or facilities, or other post-approval changes, may necessitate additional FDA review and approval. The labeling, advertising, promotion, marketing and distribution of a drug or biologic product also must be in compliance with FDA requirements relating to, among others, standards and regulations for direct-to-consumer advertising, communication of information relating to off-label uses, industry sponsored scientific and educational activities and promotional activities involving the Internet. The FDA has very broad enforcement authority, and failure to abide by these regulations can result a warning letter mandating the correction of deviations from regulatory standards, or enforcement actions that can include seizures, fines, injunctions and criminal prosecution.

Fast track and orphan drug designation

The FDA has a “fast track” program allows for expedited review of an application. However, there is no assurance that the FDA will, in fact, accelerate the review process for a fast track product candidate. Fast track status is provided only for new and novel therapies that are intended to treat persons with life-threatening and severely debilitating diseases, where there is a defined unmet medical need, particularly when no satisfactory alternative therapy exists or the new therapy is significantly superior to alternative therapies. During the development of product candidates that qualify for this status, the FDA may expedite consultations and reviews of these experimental therapies. The FDA can base its approval of an application for a fast track review on an effect on a clinical endpoint, or on a surrogate endpoint that is reasonably likely to predict clinical benefit. The FDA may condition the approval of an application for certain fast track products on additional post-approval studies to validate the surrogate endpoint or confirm the effect on the clinical endpoint. Fast track status also provides the potential for a product candidate to have a “priority review.” A priority review allows for portions of the application to be submitted to the FDA for review prior to the completion of the entire application, which could result in a reduction in the length of time it would otherwise take the FDA to complete its review of the application. Fast track status may be revoked by the FDA at any time if the clinical results of a trial fail to continue to support the assertion that the respective product candidate has the potential to address an unmet medical need. A product approved under a “fast track” designation is subject to expedited withdrawal procedures and to enhanced FDA scrutiny of promotional materials.

The FDA may grant orphan drug status to drugs intended to treat a “rare disease or condition,” which is generally a disease or condition that affects fewer than 200,000 individuals in the United States. If and when the FDA grants orphan drug status, the generic name and trade name of the therapeutic agent and its potential orphan use are publicly disclosed by the FDA. Aside from guidance concerning the non-clinical laboratory studies and clinical investigations necessary for approval of the application, orphan drug status does not convey any advantage in, or shorten the duration of, the regulatory review and approval process. The FDA may grant orphan drug designations to competing product candidates targeting the same uses. A product that has been designated as an orphan drug that subsequently receives the first FDA approval for the designated orphan use is entitled to orphan drug exclusivity, which means that, except in very limited circumstances, the FDA may not approve any other applications to market a drug for the same indication for seven years from the date of FDA approval. Orphan drug status may also provide certain tax benefits. Finally, the FDA may fund the development of orphan drugs through its grants program for clinical studies.

The FDA has designated defibrotide as an orphan drug for the treatment of severe VOD and the prevention of VOD and has provided funding for clinical studies for defibrotide to treat VOD. The FDA has approved our application for “fast track” designation for defibrotide to treat severe VOD occurring after stem cell transplantation by means of injection. If our other product candidates meet the criteria, we may apply for orphan drug status and fast track status for these other products.

Market Exclusivity

In addition to orphan drug exclusivity, a product regulated by the FDA as a “new drug” is potentially entitled to non-patent and/or patent exclusivity under the Federal Food, Drug and Cosmetic Act, or FFDCA, over a third party obtaining an abbreviated approval of a generic product during the exclusivity period. An abbreviated approval allows an applicant to obtain FDA approval without generating, or obtaining a right of reference to, the basic safety and effectiveness data necessary to support the initial approval of the drug product or active ingredient. In the case of a new chemical entity (an active ingredient which has not been previously approved with respect to any drug product) non-patent exclusivity precludes an applicant for abbreviated approval from submitting an abbreviated application until five years after the date of approval of the new chemical entity. In the case of any drug substance (active ingredient), drug product (formulation and composition) and method of use patents listed with the FDA, patent exclusivity under the FFDCA precludes the FDA from granting effective approval of an abbreviated application of a

generic product until the relevant patent(s) expire, unless the abbreviated applicant certifies that the relevant listed patents are invalid, not infringed or unenforceable and the NDA/patent holder does not bring an infringement action within 45 days of receipt of notification of the certification or an infringement action is brought within 45 days and a court determines that the relevant patent(s) are invalid, not infringed or unenforceable or 30 months have elapsed without a court decision of infringement.

User Fees

A New Drug Application for a prescription drug product that has been designated as an orphan drug is not subject to the payment of user fees to the FDA unless the application includes an indication other than the orphan indication.

A supplement proposing to include a new indication for a designated orphan disease or condition in an application is also not subject to a user fee if the drug has been designated an orphan drug with regard to the indication proposed in such supplement.

There is no specific exemption for orphan drug products from annual product and establishment fees. However, sponsors of orphan drugs can request a waiver of such fees on hardship or other grounds.

HIPAA

Other federal legislation may affect our ability to obtain certain health information in conjunction with our research activities. The Health Insurance Portability and Accountability Act of 1996, or HIPAA, mandates, among other things, the adoption of standards designed to safeguard the privacy and security of individually identifiable health information. In relevant part, the U.S. Department of Health and Human Services, or HHS, has released two rules to date, which mandate the use of new standards with respect to such health information. The Privacy Rule imposes new standards relating to the privacy of individually identifiable health information. These standards restrict the manner and circumstances under which covered entities may use and disclose protected health information so as to protect the privacy of that information. The second rule released by HHS establishes minimum standards for the security of electronic health information. In addition, the American Recovery and Reinvestment Act of 2009, or ARRA, imposes additional requirements for covered entities to protect individually identifiable health information. While we do not believe we are directly regulated as a covered entity under HIPAA, the HIPAA standards and requirements under ARRA impose requirements on covered entities, including those covered entities that conduct research activities regarding the use and disclosure of individually identifiable health information. As a result, unless they meet these HIPAA and ARRA requirements, covered entities conducting clinical trials for us may not be able to share with us any results from clinical trials that include such health information.

Foreign Regulatory Approval

Outside of the United States, our ability to market our product candidates will also be contingent upon our receipt of marketing authorizations from the appropriate foreign regulatory authorities, regardless of whether or not FDA approval has been obtained. The foreign regulatory approval process in most industrialized countries generally involves risks similar to those associated with the FDA approval process, as described herein. The requirements governing the conduct of clinical trials and marketing authorizations, and the time required to obtain requisite approvals may widely vary from country to country and may differ from that required for FDA approval.

European Union Regulatory Approval

Under the current European Union regulatory system, applications for marketing authorizations may be submitted under either a centralized or decentralized procedure. Under the centralized procedure (which is compulsory for certain categories of drugs) the grant of a single marketing authorization will be recognized as valid in all European Union member states. The decentralized procedure provides for mutual recognition of national approval decisions. Under the latter procedure, the holder of a national marketing authorization, obtained in accordance with the procedural requirements applicable in the member state concerned, may submit an application to the remaining member states in which it seeks a marketing authorization. Within 90 days of receipt of the application and assessment report, each member state must decide whether or not to recognize approval. The mutual recognition process results in separate national marketing authorizations in the reference member state and each concerned member state.

The centralized procedure

An applicant under the centralized procedure must be a person who is domiciled in the European Union or an entity established in the European Union. The applicant must file a preliminary request containing information regarding the product candidate, including a description of the product applicant and the location of the production plant, along with payment of the application fees. The European Medicines Agency (a European Union statutory entity) formally evaluates the preliminary request and either indicates initial approval or a rejection of the preliminary request. If the European Medicines Agency indicates an initial approval of the preliminary request, the applicant must then submit a full application to the European Medicines Agency for review. This application must indicate certain specific information regarding the product candidate, including the composition (quality and quantity) of all the substances contained in the product, therapeutic indications and adverse events, modalities of use, the results of physical, chemical, biological and microbiological tests, pharmacological and toxicity tests, clinical tests, a description of production and related control procedures, a summary of the characteristics of the product as required by the European legislation and samples of labels and information to consumers. The applicant must also file copies of marketing authorizations obtained, applications filed and denials received for the same product in other countries, and must prove that the manufacturer of the product candidate is duly authorized to produce it in its country.

The European Medicines Agency (through its internal Committee for Proprietary Medicinal Products For Human Use) examines the documents and information filed and may carry out technical tests regarding the product, request information from the member state concerned with regard to the manufacturer of the product candidate and, when it deems necessary, inspect the manufacturing facility in order to verify that the manufacturing facility is consistent with the specifications of the product candidate, as indicated in the application.

The Committee generates and submits its final opinion to the European Commission, the member states and the applicant. The Commission then issues its decision, which is binding on all member states. However, if the Commission approves the application, member states still have authority to determine the pricing of the product in their territories before it can be actually marketed.

The European Medicines Agency may reject the application if the Agency decides that the quality, safety and effectiveness of the product candidate have not been adequately and sufficiently proven by the applicant, or if the information and documents filed are incomplete, or where the labeling and packaging information proposed by the applicant does not comply with the relevant European rules.

The European Medicines Agency has also established an accelerated evaluation procedure applicable to product candidates intended to treat or prevent serious diseases or conditions for which no suitable therapy exists, and for which substantial beneficial effects on patients can be predicted.

The marketing authorization is valid for five years and may be renewed, upon application, for additional five year terms. After the issue of the authorization, the holder must constantly take into consideration scientific and technical progress so that the product is manufactured and controlled in accordance with generally accepted scientific methods.

We plan to submit applications for approval of our product candidates under the centralized procedure. We believe that the centralized procedure will result in quicker approval of our product candidates than will the decentralized procedure due to the fact that we intend to market our product candidates in many European Union member states, as opposed to a single member state.

The decentralized procedure

The decentralized procedure provides for mutual recognition of national approval decisions. Under this procedure, the holder of a national marketing authorization, obtained in accordance with the procedure and requirements applicable in the member state concerned (see the description below for Italy), may submit an application to the remaining member states in which it seeks a marketing authorization. Within 90 days of receipt of the application and assessment report, each member state must decide whether or not to recognize approval. The mutual recognition process results in separate national marketing authorizations in the reference member state and each concerned member state

An application under the decentralized procedure begins with the applicant obtaining a national marketing authorization. An outline of the process for obtaining a national marketing authorization in Italy is set forth below. The applicant then submits an application for authorization to other member states and the European Medicines Agency. If any of member state refuses to recognize the authorization by the original member state, the matter is deferred to arbitration proceedings, unless the applicant withdraws its request in the member state refusing recognition. The characteristics of the product in the new applications must be identical to those approved in the original member state

Post-approval issues

There are many national legislative instruments (implementing European Union rules) governing controls on drugs in the post-authorization phase. For instance, the holder of the national marketing authorization must promptly record in detail any adverse reaction to the drug of which it becomes aware, regardless of the country in which the reaction occurs, and prepare periodic update reports on these adverse events. For these and other purposes, the holder of the authorization must hire and retain for its organization an expert who will be responsible for drug controlling and reporting activities.

Moreover, any form of information and advertising aimed at promoting the sale of drugs is governed by specific national legislation (also implementing European Union rules), which sets the standards for and limitations on advertising messages in general, and specific promotional activities, such as the organization of conferences regarding certain drugs and the distribution of free samples.

The export of drugs (other than plasma and blood-related products) from Italy is not subject to authorization, but the import of drugs into Italy from non-European Union countries is subject to authorization by the Ministry of Health, on the basis of the adequacy of the quality controls to be carried out on the imported drugs.

Pediatric Investigation Plan

The pediatric investigation plan, or PIP, is a key element in the European pediatric regulations and came into effect in January 2007. The PIP is a plan for defining the use of a medicinal product across all age groups of the pediatric population and across all indications. The pediatric committee, or PDCO, is a body within EMA responsible for overseeing the requirements of the pediatric regulation. The PDCO may issue a waiver with respect to the use of a medicinal product in certain (or all) indications and/or certain (or all) pediatric age groups, or it may issue a deferral of the start or completion dates of all or some of the studies in the PIP. If a sponsor complies with a PIP agreed by PDCO, the sponsor may be eligible for a six-month extension on patents covering the product described in the plan. If the product has been designated an orphan drug by EMA, it may be eligible for an additional two years of market exclusivity even if a pediatric indication is not approved.

European orphan drug status

European legislation provides for a particular procedure for the designation of medicinal products as orphan drugs. Such a designation may include incentives for the research, development and marketing of these drugs, and allows for an extended period of market exclusivity in the event of a later successful application for a marketing authorization regarding the therapeutic indications for which orphan status was awarded.

A medicinal product, during any stage of its development but, in any case, prior to the filing of any application for the marketing authorization, may be designated as an orphan drug if the person/entity that has applied for the designation can establish that it is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting no more than five persons out of every ten thousand persons in the European Union, or that it is intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition in the European Union and, without incentives, it is unlikely that the marketing of the medicinal product within the European Union would generate sufficient income to justify the necessary investments in the relevant medicinal product. Moreover, the sponsor must prove that no satisfactory method of diagnosis, prevention or treatment of the condition in question has been authorized in the European Union or, if a satisfactory method exists and has been authorized, that the medicinal product will be of significant benefit to those affected by that condition.

In order to obtain the designation of a medicinal product as an orphan drug, the sponsor shall submit an application to the European Medicines Agency for the Evaluation of Medical Products, which must describe the indication of the active ingredients of the medicinal product, the proposed therapeutic indications and proof that the criteria established by the relevant European legislation are met.

The European Medicines Agency reviews the application and prepares a summary report to a special Committee for Orphan Medicinal Products, which issues an opinion within 90 days of the receipt of the application. The European Commission must adopt a decision within 30 days of the receipt of the committee's opinion. If the European Commission approves the application, the designated medicinal product is entered in the European Register of Orphan Medicinal Products and the product becomes eligible for incentives made available by the European Union, and by member states, to support research into, and development and availability of, orphan drugs.

After registration, the product sponsor must submit an annual report to the European Medicines Agency describing the state of development of the designated orphan drug. A designated orphan drug may be removed from the Register of Orphan Medicinal Products in three cases:

- at the request of the sponsor;
- if, before the market authorization is granted, it is established that the requirements provided for in the European orphan drug legislation are no longer being met; or
- at the end of the period of market exclusivity (as explained below).

Orphan drug market exclusivity means that the European Union shall not, for a period of 10 years from the grant of the marketing authorization for an orphan drug, accept any other application for a marketing authorization, grant a marketing authorization or accept an application to extend an existing marketing authorization, for the same product. This period, however, may be reduced to six years if at the end of the fifth year it is established that the criteria set forth in the legislation are no longer met by the orphan drug, or if the available evidence shows that the orphan drug is sufficiently profitable, so that market exclusivity is no longer justified.

However, as an exception to orphan drug market exclusivity, a marketing authorization may be granted for the same therapeutic indications to a similar medicinal product if:

- the holder of the marketing authorization for the orphan drug has given his consent to the second applicant;
- the holder of the marketing authorization for the orphan drug is unable to supply sufficient quantities of the latter; or
- the second applicant can establish in its application that the second medicinal product, although similar to the authorized orphan drug, is safer, more effective or otherwise clinically superior to the orphan drug.

Raw Materials

Many of our products and product candidates are produced from DNA extracted from pig intestines, using well-established processes that are used by others to manufacture various drugs. In particular, defibrotide is derived from swine intestinal mucosa and sulglicotide is derived from swine duodenum. In 2004, we entered into supply agreements with La.bu.nat. S.r.l. for La.bu.nat. to supply us with the swine intestinal mucosa and swine duodenum we need to produce defibrotide and sulglicotide.

The contract term of the swine intestinal mucosa supply agreement expires on December 31, 20123, with automatically renewable three year periods, unless either party notifies the other party in writing six months prior to the annual date of termination.

The contract term of the swine duodenum supply agreement expires on December 31, 2013, with automatically renewable three year periods, unless either party notifies the other party in writing six months prior to the annual date of termination.

While we currently do not have arrangements with any other supplier for this critical raw material, we believe there are suitable alternative sources of pig intestine. The FDA and other regulatory bodies may evaluate La.bu.nat.'s or any other supplier's processing centers in connection with the approval of our product candidates and the ongoing production of our products.

Our other product, urokinase, is derived from human urine, which is subject to similar regulatory review. We currently purchase the urine from only one supplier with whom we do not have a fixed supply agreement, although we believe there are suitable alternative sources of this material.

Historically, there has been no significant price volatility for any of our raw materials. It is possible, however, that widespread illness or destruction of pigs could result in volatility of the price of pig intestines.

Competition

Our industry is highly competitive and characterized by rapid technological change. Significant competitive factors in our industry include:

- manufacturing cost control;
- the effectiveness and safety of products;
- the timing and scope of regulatory approvals;
- the willingness of private insurance companies and government sponsored health care programs to reimburse patients or otherwise pay for the drugs and the related treatments;
- the availability of alternative treatments for the disorders that the drugs are designed to treat or prevent, as well as the availability of alternatives to the treatments which cause or contribute to these disorders (such as chemotherapy, radiation therapy, stem cell transplants, etc.);
- the ability to perform clinical trials, independently or with others;
- intellectual property and patent rights and protections; and

- sales and marketing capabilities.

We face competition in the product candidate development and marketing arenas. During development, the existence or discovery of alternative treatments for similar or completely different disorders may limit our ability to acquire participants or co-sponsors in connection with clinical trials for our product candidates. Any product candidates that we successfully develop that are approved for sale by the FDA or similar regulatory authorities in other countries may compete with products currently being used or that may become available in the future. There may be organizations, including large pharmaceutical and biopharmaceutical companies, such as Genzyme Corp., Millennium Pharmaceuticals, Inc., Otsuka Pharmaceutical Co., Ltd., Eisai Co., Ltd., and Celgene Corp, as well as academic and research organizations and government agencies, who are interested in pursuing the research and development of drug therapies that target the blood vessel wall. Many of these organizations have substantially greater capital resources than we have, and greater capabilities and resources to conduct basic research, preclinical studies and clinical trials, regulatory affairs, manufacturing, marketing and sales. As a result, our competitors may develop or license products or other novel technologies that are more effective, safe or cost efficient than our existing products or products that we are developing, or may obtain regulatory approval for products before we do. Clinical development by others may render our products or product candidates noncompetitive.

While we are unaware of any other products or product candidates that treat or prevent VOD, we believe that other companies have products or are currently developing products to treat some of the same disorders and diseases that our other product candidates are designed to treat.

Our statements above are based on our general knowledge of and familiarity with our competitors.

Legal Proceedings

Currently, we are not a party to or engaged in any material legal proceedings.

ORGANIZATIONAL STRUCTURE

We were part of a group of pharmaceutical businesses founded in Italy in 1944 that has been involved in the research and development of drugs derived from DNA and DNA molecules since the 1970's. In 1993, we were formed by FinSirton as Pharma Research S.r.L., an Italian private limited company, for the purpose of pursuing research and development activities of prospective pharmaceutical specialty products. FinSirton is our largest shareholder, and may be deemed to be controlled by Dr. Laura Ferro, our former Chief Executive Officer and President and a current member of our board of directors, together with her family. In December 2000, we converted into a corporation and in July 2001 we changed our name to Gentium S.p.A. Under our current bylaws, the duration of our existence will expire on December 31, 2050. We have no subsidiaries, but do have representative offices in the United States and in Switzerland.

PROPERTY, PLANT AND EQUIPMENT

Manufacturing and Facilities

We own a manufacturing facility near Como, Italy which, at December 31, 2010, is subject to a mortgage securing repayment of an aggregate of €1.8 million of debt owed to Banca Nazionale del Lavoro. The manufacturing facility is 2,350 square meters in size. In order to obtain FDA approval for the sale of any of our product candidates, the FDA must determine that this facility meets its current good manufacturing practices, or GMPs, including requirements for equipment verification of our manufacturing and cleaning processes. The FDA has not yet inspected our facility, but since 2004 we have spent more than €10 million on upgrades to our facility in anticipation of such inspection.

We produce defibrotide and sulglicotide at this facility and have the capability to produce sodium heparin. In 2006, we replaced a principal reactor in the defibrotide production line and separated the defibrotide production line from the sulglicotide line by installing an additional reactor. These improvements allow us to produce both defibrotide or sodium heparin and sulglicotide simultaneously and to double our potential capacity to manufacture defibrotide and sulglicotide.

We typically operate our manufacturing facility on two eight hour shifts per day. We work seven days per week. Our estimated current production, maximum production capacity, and percentage of utilization for defibrotide for the fiscal year 2011 are set forth below:

Product	Estimated Current Production Levels (kilograms/year)	Maximum Production Capacity With Two Eight Hour Shifts (kilograms/year)	Percentage of Utilization	
Defibrotide	180	4,400	4	%

Until December 31, 2008, we manufactured defibrotide for the treatment and prevention of vascular disease with risk of thrombosis, to be filled and finished and sold in Italy under the trademarks Prociclide and Noravid. We have discontinued the manufacture of defibrotide for this use; however, we will continue to manufacture defibrotide to meet future demands and for clinical trials and named-patients and cost recovery programs.

Our estimated current production, production capacity, and percentage of utilization for sulglicotide for the fiscal year 2011 are set forth below:

Product	Estimated Current Production Level (kilograms/year)	Maximum Production Capacity With Two Eight Hour Shifts (kilograms/year)	Percentage of Utilization	
Sulglicotide	8,626	8,626	100	%

Our estimated current production, production capacity, and percentage of utilization for urokinase for the fiscal year 2011 are set forth below:

Product	Estimated Current Production Level (millions of units/year)	Maximum Production Capacity With One Eight Hour Shift (millions of units/year)	Percentage of Utilization	
Urokinase	39,600	39,600	100	%

Our facility is subject to the regulation of regional agencies regarding worker health and safety, the fire department, and Azienda Sanitaria Locale and Agenzia Regionale Prevenzione e Ambiente with respect to water, air, noise and environmental pollution protection. We have engaged Lariana Depur, a consortium that specializes in the treatment of waste water, to treat our waste water. We monitor our waste water to control the levels of nitrogen, chlorides and chemical oxygen before delivering the waste water to Lariana Depur for additional treatment. We do not expect any to encounter difficulties complying with these regulations. We have also installed two scrubbers to reduce the odors and chemicals released into the air by the facility to comply with Italian regulations.

The environmental management system was certified under the UNI EN ISO 14001 Standard on April 20, 2007 and the EMAS certification was obtained on July 26, 2007. Our environmental policy is designed to comply with current regulations on environmental protection, to provide for continuous improvement of our manufacturing performance, to protect our employees' health, to protect the safety of people working at our location and to respect the safety of people living close to our plant and the surrounding community.

We lease 2,350 square meters of office and laboratory space from FinSirton. In addition, we lease 100 square meters of laboratory and manufacturing space for urokinase from Sirton.

ITEM 4A. UNRESOLVED STAFF COMMENTS

None.

ITEM 5. OPERATING AND FINANCIAL REVIEW AND PROSPECTS

You should read the following discussion together with the financial statements, related notes and other financial information included elsewhere in this annual report. This discussion may contain predictions, estimates and other forward-looking statements that involve risks and uncertainties, including those discussed under "Risk Factors" and elsewhere in this annual report. These risks could cause our actual results to differ materially from any future performance suggested below.

30

OPERATING RESULTS

Overview

We are a biopharmaceutical company focused on the development and manufacture of our primary product candidate, defibrotide, an investigational drug based on a mixture of single-stranded and double-stranded DNA extracted from pig intestines. Our development of defibrotide has been focused on the treatment and prevention of a disease called hepatic veno-occlusive disease, or VOD, a condition that occurs when veins in the liver are blocked as a result of cancer treatments, such as chemotherapy or radiation, that are administered prior to stem cell transplantation. Severe VOD is the most extreme form of VOD and is linked to multiple-organ failure and high rates of morbidity and mortality.

We have completed two clinical trials, a Phase III trial of defibrotide for the treatment of severe VOD in the U.S., Canada and Israel and a Phase II/III pediatric trial in Europe for the prevention of VOD. Defibrotide has been given "orphan" status by the FDA and EMA, which means that we will have limited market exclusivity upon regulatory approval. Defibrotide has also been granted "fast-track product" designation by the FDA for the treatment of VOD. While we have not yet obtained regulatory approval to market defibrotide, we are authorized to distribute defibrotide on a pre-approval basis under a treatment Investigational New Drug, or IND, protocol, which we call our cost recovery program, in the U.S. and through a named-patient program throughout the rest of the world. We do not know of any FDA or EMA approved treatments for VOD.

We have completed certain preclinical and clinical studies requested by regulatory authorities. As part of our overall strategy, we anticipate filing for regulatory approval for defibrotide in the U.S. and Europe by the end of our second quarter in 2011. We are also working on our U.S. regulatory strategy with our commercial partner, Sigma-Tau Finanziaria S.p.A. and its affiliate, Sigma-Tau Pharmaceuticals, Inc., to which we have licensed our commercial rights to use defibrotide for both the treatment and prevention of VOD in the Americas. We are currently establishing our European sales force, as we intend to commercialize defibrotide in the major European countries on our own.

We have a manufacturing plant in Italy where we produce active pharmaceutical ingredients, which are subsequently used to make the finished forms of various drugs. We believe that we are the sole worldwide producer of defibrotide. In addition to defibrotide, we manufacture urokinase and sulglicotide, both of which are sold to third parties. All of the Company's operating assets are located in Italy.

Historically, we sold defibrotide as an active pharmaceutical ingredient to our affiliate, Sirton, who then filled and finished the defibrotide active pharmaceutical ingredient into ampoule and capsule forms. Sirton then sold these ampoules and capsules to Crinos S.p.A., a subsidiary of Stada Arzneimittel AG. Crinos, pursuant to a distribution agreement entered into with us, sold these products throughout Italy, under the trademarks Prociclide and Noravid, to treat and prevent vascular disease with risk of thrombosis in Italy.

In 2007, our relationship with Sirton changed from a customer to a contract manufacturer relationship, and we sold the finished forms of Prociclide and Noravid to Crinos directly. On December 31, 2008, the distribution agreement with Crinos expired and, keeping consistent with our overall strategy, we elected not to renew this agreement and discontinued the manufacture of defibrotide to be finished into Prociclide and Noravid. In August 2009, the Italian Health Agency accepted our request to withdraw the marketing authorization for Prociclide and Noravid, but granted an extension of the marketing authorization through May 2010 in order to sell products that were previously distributed. Subsequently the marketing authorization was terminated.

In 2009 we launched a named-patient program, administered by IDIS Limited, and a cost recovery program, administered by US Oncology Clinical Development. Both of these programs are designed to provide defibrotide to

patients on a pre-approval compassionate use basis. For the years ended December 31, 2009 and 2010, sales of defibrotide through these programs amounted to approximately 51% and 67% of our total product sales, respectively.

In January 2010, we amended and expanded our existing license agreement with Sigma-Tau Pharmaceuticals, Inc. to include the prevention indication of defibrotide for the Americas. Following this amendment, we decided to close our New York office and consolidate our corporate activities to our headquarters in Italy.

Historically, we have also generated revenue from research and development agreements with co-development partners, from the sale of rights to our intellectual property, and from licensing agreements. Our licensing agreements have included up-front payments (some of which payments are made on the basis of achievement of defined milestones), reimbursement of research and development expenses, and royalties from product sales in the licensed territories. Our revenue sources are detailed categorically below:

	For The Years Ended December 31,		
(in thousands)	2008	2009	2010
Product sales:			
Prociclide and Noravid	€ 1,728	€ -	€ -
Urokinase	844	1,974	1,893
Sulglicotide	2,672	2,789	4,640
Other	199	35	-
Named-patient/cost recovery program sales	-	4,904	13,182
Total product sales	5,443	9,702	19,715
Other revenues	1,995	466	4,836
Total revenue	€ 7,438	€ 10,168	€ 24,551

Product sales made outside Italy during the periods shown in the table above amounted to 49.1% during the year ended December 31, 2008, which were primarily sales of sulglicotide in South Korea, and 85.9% and 94.5% during the years ended December 31, 2009 and 2010 respectively, which were sales of sulglicotide in South Korea, and 85.9% and 94.5% for the years ended December 31, 2009 and 2010, respectively, which include sales of sulglicotide in South Korea, urokinase in Spain and defibrotide through the named-patient and cost recovery programs. Substantially all of our other revenues are generated from a cost sharing arrangement with Sigma-Tau Pharmaceuticals, Inc., entered into in 2007, under which Sigma-Tau Pharmaceuticals, Inc. agreed to reimburse 50% of certain costs we incurred in our Phase III clinical trial of defibrotide to treat severe VOD, and from milestone payments under our 2001 License and Supply Agreement entered into with Sigma-Tau Pharmaceuticals, Inc.

In 2010, we have been cash flow positive, primarily due to the upfront payment received from Sigma-Tau Pharmaceuticals, Inc. in connection with the expansion of the license for defibrotide in the Americas, together with revenue generated from the cost recovery and named-patient programs. We expect that existing cash and cash equivalents together with the anticipated cash flow from product sales will be sufficient to support our current operations for at least the next twelve months. However, if we are unable to obtain regulatory approval to commercialize defibrotide, unable to continue to generate revenue through our cost recovery and named-patient programs as expected, or if we are required to fund additional clinical trials, or if our cash requirements exceed our current expectation, we may incur net losses and may have to obtain additional capital through equity or debt financings, loans and collaborative agreements with corporate partners, which may not be available to us on favorable terms, if at all.

As of December 31, 2010, substantially all of our cash and cash equivalents were held in accounts at financial institutions located in the Republic of Italy and the United States, which we believe are of acceptable credit quality. We invest our cash in liquid instruments that meet high credit quality standards and generally mature within three months of the purchase date. We are exposed to exchange rate risk with respect to certain of our cash balances and accounts receivables that are denominated in U.S. dollars. As of December 31, 2010, we held a cash balance of $1.92 million, receivables of $1.37 million and payables of $1.39 million that were denominated in U.S. dollars. These dollar-based balances are available to be used for future purchases and other liquidity requirements that may be denominated in such currency. We are exposed to unfavorable and potentially volatile fluctuations of the U.S. dollar against the Euro (our functional currency).

Any increase (decrease) in the value of the U.S. dollar against the Euro will result in unrealized foreign currency remeasurement losses (gains) with respect to the Euro. The value of the Euro against the U.S. dollar and other currencies may fluctuate and is affected by, among other things, changes in political and economic conditions. Any change in the value of the Euro relative to the currencies in which we transact business in the future could materially and adversely affect our cash flows, revenues and financial condition. To the extent that we hold assets denominated in U.S. dollars, any appreciation of the Euro against the U.S. dollar could result in a non-cash charge to our operating results and a reduction in the value of our U.S. dollar denominated assets upon remeasurement.

In addition, we are exposed to foreign currency risks to the extent that we engage in transactions, such as investments, programming costs and accounts payable, denominated in currencies other than our functional currency. With respect to these items, changes in the exchange rate will result in unrealized or realized foreign currency transaction gains and losses upon settlement of the transactions.

We are exposed to changes in interest rates primarily as a result of our borrowings. Our primary exposure to variable rate debt is through the EURIBOR and we have entered into interest rate cap agreements to manage exposure interest rate movement. Interest rate cap agreements lock in a maximum interest rate, enabling us to benefit from lower interest rates in the event that the variable rates rise.

Critical Accounting Policies and Estimates

Our financial statements have been prepared in accordance with accounting principles generally accepted in the United States. The preparation of these financial statements requires management to make estimates, judgments and assumptions that affect the reported amounts of assets, liabilities, revenues, expenses and related disclosures. We base our estimates and judgments on historical experience and on various other assumptions that we believe to be reasonable under the circumstances. Actual results could differ from those estimates.

We believe the following policies to be critical to the understanding our financial condition and operation results because they require us to make estimates, assumptions and judgments about matters that are inherently uncertain.

Revenue Recognition

Our primary source of revenue is from the sale of products, named-patient and cost recovery programs and from collaborative arrangements. We recognize revenue from product sales when ownership of the product is transferred to and accepted by the customer, the sales price is fixed or determinable, and collectability is reasonably assured. Provisions for returns and other adjustments related to sales are provided during the same period in which the related sales are recorded on the basis of historical rates of return. Historically, our returns have been insignificant. Revenues are recorded net of applicable allowance for contractual adjustments entered into with customers.

Collaborative arrangements generally contemplate that our technology or intellectual property will be utilized to commercialize or produce certain pharmaceutical products and that we will receive certain revenues pursuant to these agreements. Collaborative arrangements with multiple deliverables are divided into separate units of accounting if certain criteria are met, including whether the delivered element has stand-alone value to the customer and whether there is objective and reliable evidence of the fair value of the undelivered items. The consideration received from these arrangements is allocated among the separate units based on their respective fair value, and the applicable revenue recognition criteria are applied to each separate unit. Revenue associated with substantive at-risk milestones is recognized based upon the achievement of the milestones as defined in the respective agreements. We defer, and recognize as revenue, non-refundable payments received in advance that are related to the future performance over the life of the related research project. We recognize reimbursements to fund research and development efforts as such qualified expenditures are made. Finally, royalty revenues are recognized when earned after the applicable sales are made.

Inventories

Inventories consist of raw materials, semi-finished and finished active pharmaceutical ingredients and defibrotide distributed through the named-patient and treatment IND programs. We state inventories at the lower of cost or market, determining cost on an average cost basis. We periodically review inventories and reduce items to their estimated net realizable value as they become outdated or obsolete. We estimate reserves for excess and obsolete inventories based on inventory levels on hand, future purchase commitments, and current and forecast product

demand. Our reserve level and as a result our overall profitability, is therefore subject to our ability to reasonably forecast future sales levels versus quantities on hand and existing purchase commitments. Forecasting demand and resource planning are based, in part, on assumptions that we must make regarding expected market changes, overall demand, pricing incentives and raw material availability, among other variables. Significant changes in these estimates could indicate that inventory levels are excessive, which would require us to reduce inventories to their estimated net realizable value.

In the highly regulated industry in which we operate, raw materials, work in progress and finished goods inventories have expiration dates that must be factored into our judgments as to the recoverability of inventory cost. Additionally, if our estimate of a product's demand and pricing is such that we may not fully recover the cost of inventory, we must consider that in our judgment as well. We also review our inventory and the manufacturing process for quality assurance and quality control issues and determine if a write-down is necessary. In the context of reflecting inventory at the lower of cost or market, we record an inventory reserve as soon as a need for such a reduction in net realizable value is determined.

Prior to commencing the sale of defibrotide through the named-patient and cost recovery programs, we had expensed all costs associated with the production of defibrotide as research and development expenses. Subsequent to signing the agreements associated with the named-patient and cost recovery programs, we began to capitalize the costs of manufacturing defibrotide as inventory, including costs to convert existing raw materials to active pharmaceutical ingredient and costs to package and label previously manufactured inventory, which costs had already been expensed as a research and development expense. Until we sell the inventory for which a portion of the costs were previously expensed, the carrying value of our inventories and our cost of sales will reflect only incremental costs incurred subsequent to the signing of these agreements.

We expense costs relating to the production of clinical products as a research and development expense in the period incurred, which are not expected to be sold through the named-patient and cost recovery programs. We will continue to do so until we receive an approval letter from the FDA or EMA for a new product or product configuration. Upon receipt of an approval letter from FDA or EMA for a new product or product configuration, we will begin to capitalize the subsequent inventory costs relating to that product configuration.

Impairment of Long-lived Assets

Our long-lived assets consist primarily of property and equipment. We evaluate our ability to recover the carrying value of long-lived assets used in our business, considering changes in the business environment or other facts and circumstances that suggest their value may be impaired.

If, based on the preceding discussion, our management has concluded that impairment indicators exist, we will initially review this by assessing the undiscounted cash flows expected to be derived from the asset or group of assets, comparing the lowest level of total expected undiscounted cash flow to the carrying value. If the carrying value of the asset or group of assets exceeds the sum of the undiscounted cash flows, impairment is considered to exist. An impairment charge is assessed by comparing the assets fair value to its carrying value. Fair value can be calculated using a number of different approaches, including discounted cash flow, comparables, and market valuations or quoted market prices. The process and steps required to assess the possible impairments of assets, including the identification of possible impairment indicators, an assessment of undiscounted cash flows, the selection of an appropriate discount rate, the calculation of the weighted average cost of capital and the discounts or premiums inherent in market prices require a substantial amount of management discretion and judgment. If actual results differ from these estimates, or if we adjust these estimates in future periods, operating results could be significantly affected.

Research and Development Expenses

Several of our activities and related costs are designated research and development expenses, which primarily include salary and benefits payments to our direct employees, employee stock-based compensation expenses, facility costs, overhead costs, clinical trial costs and related trial product manufacturing costs, contracted services and subcontractor costs. Clinical trial costs include costs associated with contract research organizations. The billings we receive from contract research organizations for services rendered may not be received for several months following the service. We accrue the estimated costs of the contract research organizations' related services based on our estimate of management fees, site management and monitoring costs and data management costs. Our research and development department is in constant communication with our contract research organizations to assess their progress on the underlying study and the reasonableness of their cost estimates. Differences between estimated trial costs and actual costs have not been material to date, and any changes have been made when they become known. Under this policy, research and development expenses can vary due to accrual adjustments related to the underlying clinical trials and the expenses incurred by the contract research organizations. At December 31, 2010, we had €0.64 million of future payables under outstanding contracts with various contract research organizations that are not revocable. Most of these contracts are on a cost plus or actual cost basis.

Stock-Based Compensation

Employee stock-based compensation is estimated on the date of grant, based on the fair value of the employee stock award. Employee stock-based compensation is recognized ratably over the requisite service period, which is generally the vesting period, in a manner similar to other forms of compensation paid to employees.Historically, the fair value of all option grants were estimated on the grant date using the Black-Scholes option-pricing model. For all stock options granted after December 31, 2009, the fair value of the award is estimated on the date of grant using a binomial valuation model. The binomial model considers characteristics of fair value option pricing that are not available under the Black-Scholes model. Similar to the Black-Scholes model, the binomial model takes into account variables such as volatility, dividend yield rate, and risk free interest rate. However, unlike the Black-Scholes model, the binomial model also considers the contractual term of the option, the probability that the option will be exercised prior to the end of its contractual life, the probability of termination or retirement of the option holder in computing the value of the option, and the exchange rate between the euro and the dollar, a variable which had a greater impact on the option exercise price in 2010. For these reasons, the Company believes that the binomial model provides a fair value that is more representative of actual experience and future expected experience than that value calculated using the Black-Scholes model.

The option-pricing model requires the use of certain subjective assumptions or estimates regarding the expected volatility of the market price of our stock, the expected term of the award and the expected forfeiture rate. In estimating the expected term of an award, we consider the vesting period of the award, our historical experience with employee stock option exercise and the expected volatility and use relevant peer group data as a comparative measure.

We review our assumptions periodically and we may change the assumptions we use to value share-based awards granted in future periods. Such changes may lead to a significant change in the expenses we recognize in connection with share-based payments.

In using the option pricing model that we have selected, changes in the underlying assumptions have the following effect on the resulting fair value output:

An increase to the:	Results in a fair value estimate that is:
Price of the underlying share	Higher
Exercise price of option	Lower
Expected volatility of stock	Higher
Risk-free interest rate	Higher
Expected term of option	Higher

In our current valuation, we consider the volatility factor to be an important factor in determining the fair value of the options granted. We have used a 92.59% factor based on what we believe is a representative sample of similar biopharmaceutical companies. However, this sample is not perfect, as it omits, for example, Italian companies, due to the fact that there is a limited number of companies such as ourselves publicly traded in the U.S. market. Significant changes to these estimates could have a material impact on the results of our operations.

Tax Loss Carryforwards

As of December 31, 2010 and 2009, we had net operating loss (NOL) carryforwards of approximately €54.51 million and €56.20 million, respectively.

As required by ASC 740, our management has evaluated the positive and negative evidence bearing upon the ability to realize our deferred tax assets, which are comprised principally of NOL and research and experimentation credit carryforwards. Management has determined at this time that it is more likely than not that we will not recognize the benefits of federal and state deferred tax assets and, as a result, a valuation allowance of approximately €23.62 million has been established at December 31, 2010.

Recent Accounting Pronouncements

Reference should be made to Note 2 of our financial statements, “Summary of Significant Accounting Policies to our Financial Statements,” for a discussion of new accounting standards.

Results of Operations

The following tables set forth our results of operations:

	For The Years Ended December 31,		
	2008	2009	2010
Amounts in thousands except share and per share data			
Revenues:			
Product sales to related party	€ 651	€ 195	€ -
Product sales to third parties	4,792	9,507	19,715
Total product sales	5,443	9,702	19,715
Other revenues	25	129	289
Other revenues from related party	1,970	337	4,547
Total Revenues	7,438	10,168	24,551
Operating costs and expenses:			
Cost of goods sold	5,596	4,002	5,786
Research and development	9,569	3,512	6,104
General and administrative	7,668	6,036	5,835
Restructuring charges	-	-	1,101
Depreciation and amortization	998	916	908
Charges from related parties	537	279	346
Write-down of assets	3,403	-	-
Total operating costs and expenses:	27,771	14,745	20,080
Operating income/(loss)	(20,333)	(4,577)	4,471
Foreign currency exchange gain, net	173	162	90
Interest income/(expense), net	256	(110)	(87)
Income/(loss) before income tax expense	(19,904)	(4,525)	4,474
Income tax expense:			
Current	-	-	(397)
Net income/(loss)	€ (19,904)	€ (4,525)	€ 4,077
Net income/(loss) per share:			
Basic and diluted net income/(loss) per share	(1.33)	(0.30)	0.27
Weighted average shares used to compute basic and diluted net income/(loss) per share	14,956,263	14,956,317	14,956,317

Year Ended December 31, 2010 Compared to Year Ended December 31, 2009

Product sales.

Product sales were €19.72 million for 2010 compared to €9.70 million for 2009, an increase of €10.02 million or 103%. The increase was primarily due to the distribution of defibrotide through the named-patient and cost recovery programs initiated in April and October 2009, respectively. For the years ended December 31, 2010 and 2009,

named-patient and cost recovery program sales amounted to €13.18 million and €4.90 million, respectively, which are net of €2.13 million and €0.79 million in service fees, respectively.

Sales to a related party, Sirton, for the years ended December 31, 2010 and 2009 represented none and 2% of the total product sales, respectively. The decrease in sales to a related party was primarily due to the fact that, in the second quarter of 2009, we terminated our supply agreement with Sirton and entered into direct sales agreements with Sirton's customers in order to mitigate the risk associated with Sirton's poor financial situation.

Sales to third parties increased from €9.51 million in 2009 to €19.72 million in 2010, an increase of €10.21 million or 107%. The increase was primarily due to the launch of the named-patient and cost recovery programs in 2009, through which sales amounted to €13.18 million for 2010 compared to €4.90 million for 2009. Excluding such sales, sales to third parties for active pharmaceutical ingredients would have been €6.54 million and €4.61 million in 2010 and 2009, respectively, an increase of €1.93 million or 42%, primarily due to the increase in volume for sulglicotide.

Other revenues

Other revenues were €4.84 million for 2010 compared to €0.47 million for 2009. The increase versus the prior year is primarily attributable to an increase in activities that were reimbursed from Sigma-Tau under a cost sharing arrangement with the Company, which amounted to €1.14 million, and a ratable recognition of €3.41 million ($4.67 million) of the €5.11 million ($7.0 million) up-front payment made by Sigma-Tau in connection with the amendment of the existing license and supply agreement with the Company. The up-front payment is being recognized ratably through the second quarter of 2011, which is when the Company expects to file a New Drug Application for defibrotide.

Cost of goods sold.

Our cost of goods sold was €5.79 million in 2010 compared to €4.00 million in 2009. The cost of goods sold as a percentage of product sales, was 29% in 2010 compared to 41% in 2009. The percentage decrease is primarily due to the higher margin on defibrotide sold through the named-patient program and price increases in the active pharmaceutical ingredients business. We wrote-off €0.37 million of inventory of heparin that may not have met good manufacturing practices.

Research and development expenses.

We incurred research and development expenses of €6.10 million in 2010 compared to €3.51 million for 2009. 2009 research and development expenses were net of €0.85 million of government grants in the form of a tax credit, accrued as reduction of expenses. Excluding such grants, 2009 research and development expenses would have been €4.36 million. The increase from the comparable period in 2009 was primarily due to completion of a technology transfer and costs associated with pre-clinical and clinical studies such as reproductive toxicity, hERG channel, QT/QTc, pharmacokinetics of defibrotide in healthy volunteers as well as regulatory consulting services associated with the completion of the eCTD.

General and administrative expenses.

Our general and administrative expenses were €5.84 million for 2010 compared to €6.04 million for 2009. 2010 and 2009 general and administrative expenses include a release of a reserve for doubtful accounts for €0.27 million and for €0.68 million, respectively, due to the offset of accounts receivable against the same amount of account payables due to the counterparty. Excluding the effect of the release of the allowance, general and administrative expenses represent a slight decrease from the prior year mainly due to the closure of the New York office, decrease in payroll costs, and lower legal and public company expenses offset by an increase in stock based compensation costs.

Restructuring charges.

Our restructuring charges were €1.10 million for 2010 compared to none for 2009. Restructuring charges of €0.95 million include one-time employee termination benefits, cost to terminate lease contracts and others exit costs resulting from a strategic decision to close down the New York office and to consolidate our resources and operations into our headquarters in Como, Italy. Additionally, we implemented a workforce reduction and recorded €0.16 million

in one-time employee termination benefits, outplacement costs, termination notice and legal contractual compensation due upon early termination of certain employments agreements.

Depreciation and amortization expense.

Depreciation and amortization expenses were €0.91 million in 2010 compared to €0.92 million in 2009. Depreciation expenses do not include the depreciation of our manufacturing facilities, which is included in our cost of goods sold.

Foreign currency exchange gain (loss), net

Our foreign currency exchange gain (loss) is primarily due to the remeasurement at December 31, 2010 of U.S. dollar cash balances, accounts receivables and payables. The net decrease is mainly due to higher unrealized unfavorable foreign exchange losses on our cash balances and accounts payables due to the fluctuation in foreign exchange rates.

Interest income/(expense), net.

Interest income/(expense), net amounted to €(0.09) million and €(0.11) million in 2010 and 2009, respectively. The net decrease in interest income/(expense), net is mainly due to a decrease in interest rates and long term debt as a consequence of the payment of the current portion of the long term debt outstanding.

Income tax expense

Income tax expenses primarily refers to the Italian Regional Tax on Productive Activities, or "IRAP," and has a floating a statutory rate of 3.9%. The IRAP tax is not deductible for corporate purposes. The IRAP tax base is similar to the corporate tax base but does not permit a deduction for labor and interest.

Net income/(loss).

Our net income was €4.08 million in 2010 compared to a net loss of (€4.53) million in 2009. The difference was primarily due to higher sales and margins associated with the named-patient and cost recovery programs and API business, increase in other income and revenues (including the ratable recognition as revenue of a portion of the up-front payment made by Sigma-Tau in connection with the amendment of the existing license and supply agreement with us), and decrease in general and administrative expense offset by an increase in research and development expenses, restructuring charges and income tax expenses.

Year Ended December 31, 2009 Compared to Year Ended December 31, 2008

Product sales.

Our product sales were €9.70 million for 2009 compared to €5.44 million for 2008, an increase of €4.26 million or 78.3%. The increase was primarily due to the launch in April 2009 of the named-patient program and the launch in September 2009 of the cost recovery program in the U.S. Named-patient program and cost recovery program sales, for the year ended December 31, 2009 amounted to €4.90 million.

Sales to a related party, Sirton, for the years ended December 31, 2009 and 2008 represented 2% and 12% of total product sales, respectively. The decrease in sales to a related party is primarily due to the fact that in the second quarter of 2009 we terminated our supply agreement with Sirton and entered into direct sales agreements with Sirton's customers in order to mitigate the risk associated with Sirton's poor financial condition. Additionally, after March 2008, we did not recognize product sales to a related party, amounting to €1.08 million, because one of the criteria stated by SAB 104 ("collectability is reasonably assured") was not met.

Sales to third parties rose to €9.51 million in 2009 compared to €4.79 million for 2008, an increase of €4.72 million or 98.5%. The increase was primarily due to the launch in 2009 of the named-patient and cost recovery programs, which amounted to €4.90 million in sales. Excluding such sales, sales to third parties related to the API business would have been €4.61 million and €4.79 million in 2009 and 2008, respectively, with a decrease of €0.18 million or 3.8%, primarily due to slight decreases in the units of sulglicotide sold, offset by the price increase and higher volume of urokinase sold in 2009 compared to the prior year.

Other revenues

Our other revenues were €0.47 million for 2009 compared to €1.99 million for 2008. The decrease versus the prior year is primarily attributable to a decrease in activities that were reimbursed from Sigma-Tau under our cost sharing agreement, offset by a milestone payment from Sigma-Tau of €0.23 million ($0.35 million) for completion of the phase

III clinical trial.

Cost of goods sold.

Our cost of goods sold was €4.00 million for 2009 compared to €5.60 million for 2008. Cost of goods sold as a percentage of product sales was 41% in 2009 compared to 103% in 2008. The percentage decrease is primarily due to higher margin on defibrotide sold through the named-patient program and price increases in the API business. The Company fully expensed the cost of inventory in the prior year. Additionally, the higher percentage of cost of goods sold in 2008 was primarily due to the fact that product sales to a related party, Sirton, were not recognized in the amount of €1.08 million due to Sirton's poor financial condition and concerns over the ability to collect such receivables.

Research and development expenses.

We incurred research and development expenses of €3.51 million in 2009 compared to €9.57 million in 2008. Research and development expenses in 2009 and 2008 are net of €0.85 and €0.79 million, respectively, of government grants in the form of a tax credit. The reduction from the prior year is a result of a decrease in the activities relating to the treatment and prevention studies.

General and administrative expenses.

Our general and administrative expenses were €6.04 million in 2009 compared to €7.67 million in 2008. In 2008, we established a reserve for doubtful accounts in the amount of €1.78 million, of which €0.68 million was released in 2009. Additionally, the Company had lower payroll costs due to temporary layoffs under a special public scheme used in Italy under the "Cassa Integrazione Guadagni" program.

Depreciation and amortization expense.

Depreciation and amortization expense was €0.92 million in 2009 compared to €1.00 million in 2008. Depreciation expense excludes depreciation of our manufacturing facilities included in our cost of goods sold.

Foreign currency exchange gain (loss), net

Our foreign currency exchange gain (loss) is primarily due to the remeasurement at December 31, 2009 of U.S. dollar cash balances. The positive result between 2008 and 2009 is due to a more favorable exchange rate in 2009 and a lower cash balance.

Interest income/(expense), net.

Interest income/(expense), net amounted to €(0.11) million and €0.26 million in 2009 and 2008, respectively. The decrease in interest income/(expense), net is a result of lower amounts of invested funds in 2009 compared to the prior period as well as a decrease in interest rates.

Net loss.

Our net loss was €4.53 million in 2009 compared to €19.90 million in 2008. The difference was primarily due to increased net sales and higher margins associated with the named-patient and cost recovery programs and a decrease in development activities related to our treatment and prevention studies.

LIQUIDITY AND CAPITAL RESOURCES

	As of December 31,	
(in thousands)	2009	2010
Cash and cash equivalents	€ 1,392	€ 8,742
Available for sale securities	263	263
Total cash and cash equivalents	€ 1.655	€ 9,005

	Years Ended December 31,		
(in thousands)	2008	2009	2010
Net cash (used in) provided by operating activities	(12,775)	(5,156)	8,237
Net cash used in investing activities	(591)	(3,986)	(205)
Net cash used in financing activities	(1,417)	(1,173)	(716)
Effect of exchange rate on cash and cash equivalents	310	216	34
Net (decrease)/increase in cash and cash equivalents	€ (14,473)	(10,099)	7,350

During 2008, we used approximately €12.78 million in cash to fund operations and working capital requirements, €1.60 million to reimburse a portion of our long term debts, short term borrowings and capital lease obligations, and €0.59 million for capital expenditures. These expenditures were funded from the following sources:

- €7.44 million in gross revenues;
- €147 million in proceeds from long term debt, and
- €25.96 million in cash available at December 31, 2007.

During 2009, we used approximately €5.16 million in cash to fund operations and working capital requirements, €1.17 million to reimburse a portion of our long term debts and capital lease obligations, and approximately €4.25 million for capital expenditures, including €4 million paid to Crinos. These expenditures were funded from the following sources:

- €9.70 million in gross revenues;
- €0.26 million in sales of marketable securities; and
- €11.49 million in cash available at December 31, 2008.

During 2010, we used approximately €8.24 million in cash to fund operations and working capital requirements, €0.72 million to reimburse a portion of our long term debts and capital lease obligations, and approximately €0.21 million for capital expenditures. In 2010, in connection with a national agreement among the Italian Bank Association and the Italian Ministry of Economics and Enterprise Organizations, we obtained a deferment on the payment of principal debt outstanding for a twelve-month period. Such benefit terminated in November 2010. In 2010, we utilized a tax credit of €1.16 million to offset social security and withholding tax due and we sustained one time employee termination benefits for €0.95 million resulting from a strategic decision to consolidate our resources and operation into our headquarters in Como.

These expenditures were funded from the following sources:

- €20.43 million in revenues and reimbursement of expenses under a cost sharing agreement entered with Sigma-Tau,;
- €5.11 ($7.00) million from an upfront payment received in connection with the amendment and expansion of the license agreement with Sigma-Tau Pharmaceuticals, Inc; and
- €1.39 million in cash available at December 31, 2009.

At December 31, 2010, we had an aggregate of €2.86 million in debt outstanding and had €8.74 million in cash and cash equivalents. Additional information on the maturity, repayment obligations and interest rate structure with respect to this debt, and on our material commitments for capital expenditures, is provided below under “Contractual Obligations and Commitments.”

We expect to devote substantial resources toward the continuation of our research and development efforts and related regulatory expenses, and we anticipate expanding our licensing and collaboration efforts and establishing our sales and marketing team. Our funding requirements will depend on numerous factors including:

- the scope and results of our clinical trials;
- whether we are able to successfully commercialize and sell defibrotide for the uses for which it is being developed;
- the advancement of other product candidates in development;
- the timing of, and the cost involved in, obtaining regulatory approvals;
- the cost of manufacturing activities;
- the costs associated with building a future commercial infrastructure;
- the costs involved in preparing, filing, taking legal action against, maintaining and enforcing patent claims and other patent-related costs, including litigation costs, and the outcome of litigation of any such claims;
- our ability to establish and maintain additional collaboration arrangements.

We do not expect our revenues to increase significantly until after we successfully obtain FDA and European regulatory marketing approval for, and begin selling, defibrotide to treat severe VOD and prevent VOD. We believe that some of the key factors that will affect our internal and external sources of cash are:

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our ability to obtain FDA and European regulatory marketing approval for, and to commercially launch, defibrotide to treat and prevent VOD;

- the receptiveness of the capital markets to financings, generally, and of biotechnology companies, specifically; and

- our ability to enter into additional collaboration arrangements with corporate and academic collaborators and the success of such relationships.

Through December 31, 2010, we had accumulated losses of approximately €95.6 million. In 2010, we have been cash flow positive, primarily due to the upfront payment received from Sigma-Tau Pharmaceuticals, Inc. in connection with the expansion of the license for defibrotide in the Americas, together with revenue generated from the cost recovery and named-patient programs. However, if we are unable to obtain regulatory approval to commercialize defibrotide, unable to continue to generate revenue through our cost recovery and named-patient programs, or if we are required to fund additional clinical trials, we may revert to operating on losses and may have to obtain additional capital through equity or debt financings, loans and collaborative agreements with corporate partners, which may not be available us on favorable terms, if at all.

Italian law sets certain limitations and restrictions on our issuance of debt securities, as described in our risk factor stating, "We are restricted under Italian law as to the amount of debt securities that we may issue relative to our equity." With some exceptions, in order to issue new equity or debt securities convertible into equity, we must increase our authorized capital through a process described in our risk factor stating, "The process of seeking to raise additional funds is cumbersome, subject to the verification of a notary public as to compliance with our bylaws and applicable law and may require prior approval of our shareholders at an extraordinary meeting."

RESEARCH AND DEVELOPMENT

We discover research and conduct the initial development of our product candidates at our facilities in Italy, and we hire consultants to do the same in other European countries and the United States. We typically conduct preclinical laboratory and animal studies of product candidates ourselves or through other research facilities. We typically engage medical centers to conduct clinical trials of our product candidates. In cases where we believe that the development costs associated with a product candidate will be substantial, we may enter into collaborative arrangements with other companies to jointly develop those product candidates. We expense research and development costs as they are incurred.

Research and Development Expenses

Our research and development expenses consist primarily of costs associated with research, preclinical development contract research organization charges, regulatory activities, laboratory supplies and materials, manufacturing, contracted services and clinical trials involving our product candidates. During the years ended December 31, 2008, 2009 and 2010, we had three major categories of research projects relating to our product candidates: defibrotide to treat VOD, defibrotide to prevent VOD and assorted other projects. The table below presents our research and development expenses by project for each of the years ended December 31, 2008, 2009 and 2010.

	For The Years Ended December 31,		
(in thousands)	2008	2009	2010
Defibrotide to treat VOD	€ 7,131	€ 641	€ 5,028
Defibrotide to prevent VOD	1,055	2,102	521
Others	1,383	769	555
Total	€ 9,569	€ 3,512	€ 6,104

In December 2005, the Dana-Farber Cancer Institute at Harvard University completed a Phase II clinical trial for defibrotide to treat severe VOD in the United States. In the second quarter of 2006, we began patient enrollment in a Phase III clinical trial for this product candidate in the United States. We do not anticipate obtaining FDA or European regulatory approval of this product candidate before 2012.

Together with the European Group for Blood and Marrow Transplantation, we have completed a Phase II/III clinical trial in Europe for defibrotide to prevent VOD in children. We do not anticipate obtaining European regulatory approval of this product candidate before 2012.

An independent Phase I/II clinical trial in Italy, involving defibrotide, in combination with melphalan, prednisone and thalidomide, to treat patients with advanced and refractory multiple myeloma, started in December 2005. The Phase I portion, which concluded in 2007, involved 24 patients in four cancer centers in Italy. The Phase II portion is scheduled to involve 50 patients in 10 cancer centers in Italy. The principal investigator is Dr. Antonio Palumbo, M.D. of the Division of Hematology, University of Turin, Italy.

We expect to continue to incur expenses relating to the development of defibrotide to treat and prevent VOD. We will need additional funds before we have completed the development of defibrotide to treat and prevent VOD. A further discussion of the risks and uncertainties associated with the development of defibrotide and certain consequences of failing successfully develop the product candidate, are set forth in the risk factors under the heading "Risks Relating to Our Business" as well as other risk factors.

Intellectual Property Rights and Patents

As of December 31, 2010, we had ten U.S. patents issued with seven U.S. patent applications pending, 32 foreign patents issued with 40 foreign patent applications pending, and one international patent application (not yet nationalized) pending. The United States Patent & Trademark Office issued a patent covering our process for manufacturing defibrotide in 1991, which expired on January 15, 2008. In April 2001, we filed a patent application with the United States Patent & Trademark Office and corresponding patent applications in certain foreign countries, for the use of defibrotide in stem cell transplants. This patent expires in 2021.

Patent rights and other proprietary rights are an important component of our business. We have sought, and intend to continue to seek, patent protection for our inventions, and we rely upon patents, trademarks, trade secrets, know-how, continuing technological innovations and licensing opportunities to develop and maintain a competitive advantage.

However, the patent positions of companies like ours involve complex legal and factual questions and, as such, the enforceability of any patents we obtain cannot be guaranteed with any degree of certainty. The patents that we hold, those licensed to us, and those that may be issued to us in the future, may be challenged, invalidated or circumvented, and may not provide the intended protections against or competitive advantages over competitors with similar technology. Furthermore, it is possible that our competitors will independently develop similar technologies or duplicate our efforts while our product candidates are in development. Because of the extensive time required to develop, test and complete a regulatory review of a product candidate, it is possible that our relevant patent rights may expire before defibrotide can be approved for sale and commercialized, or within a short time after commercialization.

OFF-BALANCE SHEET ARRANGEMENTS

We do not have any off-balance sheet arrangements.

TABULAR DISCLOSURE OF CONTRACTUAL OBLIGATIONS

Contractual Obligations and Commitments

Contractual obligations represent future cash commitments and liabilities under agreements with third parties, and exclude contingent liabilities for which we cannot reasonably predict future payment. The following chart represents our total contractual obligations, at December 31, 2010, aggregated by type (in thousands):

(in thousands)	Total	1 Year	2 Years	3 Years	4 Years	5 Years
Long-Term Debt Obligations:						
Mortgage loans	€ 1,800	400	400	400	600	
Finance loans	375	250	125	-		