



Gentium Announces Final Clinical Trial Results for Defibrotide Presented at the American Society of Hematology Conference

Defibrotide Therapy Demonstrates a Strong Trend Toward Statistical Significance in the Prevention and Treatment of VOD

VILLA GUARDIA (COMO), Italy, Dec 07, 2009 (BUSINESS WIRE) -- Gentium S.p.A. (NASDAQ: GENT) today announced final clinical trial results from the Company's Phase II/III Pediatric Prevention trial and Phase III Treatment trial for Defibrotide of Hepatic Venous Occlusive Disease (VOD), which were presented at the American Society of Hematology Conference (ASH) in New Orleans. The results of both trials strongly trended toward statistical significance. The Prevention trial demonstrated a 40% reduction in the incidence of VOD at day 30 ($p=0.0488$ Competing Risk; $p=0.0507$ Kaplan-Meier) and the Treatment trial showed an improvement in complete response from 9% in the historical control arm to 24% in the Defibrotide arm ($p=0.0148$). Defibrotide was well tolerated in both studies.

Dr. Selim Corbacioglu, Pediatrics, University of Regensburg (Germany) and Principal Investigator of the Pediatric Prevention trial reported in an oral presentation that on an intent to treat basis (ITT), Defibrotide demonstrated a 40% reduction ($p=0.0488$ Competing Risk; $p=0.0507$ Kaplan-Meier) in the incidence of VOD within 30 days after stem cell transplantation (SCT). The analysis included 356 patients; 180 patients in the prophylaxis arm and 176 patients in the control arm (see Table 1). 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; see Table 2). With regard to safety, Defibrotide was well tolerated and no difference in adverse events was observed between the two study arms.

"I believe that the results of the pediatric prevention study, which is the largest trial to date conducted in the pediatric bone marrow transplant setting, confirmed that Defibrotide is well tolerated and is effective in preventing VOD," said Dr. Selim Corbacioglu. "Additionally, we are enthusiastic that Defibrotide was able to significantly reduce the incidence and severity of acute graft versus host disease, a life threatening complication of stem cells transplants for which there are limited, effective prophylactic and treatment options. This activity is consistent with the drug's role in the protection of endothelial cells."

Dr. Paul G. Richardson, Clinical Director of the Dana-Farber Cancer Institute's Jerome Lipper Multiple Myeloma Center and Principal Investigator of the Treatment trial reported in a separate oral presentation that on an ITT basis, 24% of patients in the Defibrotide arm compared to 9% of patients in the historical control arm achieved complete response at 100 days ($p=0.0148$, see Table 3). 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 cases were selected as having an unequivocal diagnosis of 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. With regard to safety, adverse events were balanced between the historical control and treatment arms.

"I am very encouraged by the results of this trial, especially given the extremely sick patient population enrolled," said Dr. Paul Richardson. "The data generated from this trial confirms the activity of Defibrotide seen in earlier studies, with the clinical benefit reflected by a significant improvement in complete response rate, as well as a promising trend for survival. In addition, the results support its potential in less advanced stages of VOD."

"To date, Defibrotide has been evaluated for the treatment and prevention of VOD in over 1,100 patients globally across multiple clinical trials, a compassionate use program and under a treatment IND protocol," said Dr. Massimo Iacobelli, Scientific Director of Gentium. "We believe that the efficacy data generated has consistently been favorable and demonstrated an acceptable safety profile. With the final results of these two studies in hand, and other supportive data, we look forward to determining the next steps toward approval."

Defibrotide has been granted Orphan Drug status by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency to prevent and to treat VOD and Fast Track designation by the U.S. FDA for the treatment of severe VOD in recipients of stem cell transplants.

Table 1. Pediatric Prevention Study Primary Efficacy Results (incidence of VOD by Day +30)

	Defibrotide Prophylaxis	Control	P-Value (Competing Risk)	P-Value (Kaplan-Meier)
Intent to Treat	12% (22/180)	20% (35/176)	0.0488	0.0507
Per Protocol	11% (18/159)	20% (34/166)	0.0220	0.0230

Table 2. Pediatric Prevention Study GvHD and Renal Failure Results (ITT Population)

	Defibrotide Prophylaxis	Control	P-Value
Incidence of Acute GvHD by D+100 (Allogeneic SCT)	45%	63%	0.0044
Incidence of Renal Failure	1%	6%	0.0170

Table 3. Treatment Study Results

	Defibrotide	Control	P-Value (adjusted)*
Intent to Treat	24%	9%	0.0148
Complete Response (Day+100)	(24/102)	(3/32)	
Intent to Treat Mortality (Day+100)	62% (63/102)	75% (24/32)	0.0508

* Adjusted by quintiles of propensity score based on 4 stratification variables: allogeneic/autologous, adult/pediatric, 1 or 2+ SCTs, ventilator/dialysis dependence

About the Phase II/III European Pediatric Prevention Trial

The Phase 2/3 European pediatric prevention trial was a prospective, multi-center, open label, randomized clinical trial to evaluate the prophylactic use of Defibrotide in patients under 18 years of age who were undergoing stem cell transplantation and were at high risk for developing hepatic Venous Occlusive Disease (VOD). Patients randomized in the prophylaxis arm received 25 mg/kg/day of Defibrotide in four divided doses beginning at the time of conditioning and until 30 days post transplant. Patients randomized to the control arm received no VOD prophylactic therapy. Patients were permitted to receive Defibrotide as therapy if they developed VOD. The primary endpoint of the study was development of VOD within 30 days post stem cell transplantation (SCT), based on the modified Seattle criteria. A blinded independent review committee of three expert hematologists confirmed the diagnosis of VOD.

About the Phase III Treatment Trial

The Phase III, historically controlled, trial was a multi-center study evaluating Defibrotide for the treatment of severe Venous Occlusive Disease (patients with VOD and multi-organ failure) in hematopoietic stem cell transplant patients. The primary endpoint of the trial was complete response at 100 days following SCT and utilized historical controls (patients who in the past received the best therapy and supportive care available at the time, but not Defibrotide) as a comparator. Secondary endpoints included survival rate at 100 days and six months post SCT. Patients in the treatment arm received 25 mg/kg/day of Defibrotide in four divided doses. The historical control database was generated through a sequential, retrospective medical chart review, with final selection of the control group performed by an independent medical review committee (MRC). The MRC remained blinded to patient outcome data throughout the duration of the trial. Per the study protocol, data in the primary efficacy analysis were adjusted by quintiles of propensity score based on four stratification variables (allogeneic/autologous SCT,

adult/pediatric, one/two+ SCTs, and ventilator/dialysis dependence) to aid in obtaining balance between the treatment and historical control arms in a non-randomized trial.

About VOD

Veno-occlusive disease is a potentially life-threatening condition, which typically occurs as an important complication of stem cell transplantation. Certain high-dose chemo-radiation therapy regimens used as part of SCT can damage the lining cells of hepatic blood vessels and so result in VOD, a blockage of the small veins of the liver that leads to liver failure and can result in significant dysfunction in other organs such as the kidneys and lungs (so-called severe VOD). SCT is a frequently used treatment modality following high-dose chemotherapy and radiation therapy for hematologic cancers and other conditions in both adults and children. There is currently no approved agent for the treatment or prevention of VOD in the U.S. or the EU.

About Gentium

Gentium, S.p.A., located in Como, Italy, is a biopharmaceutical company focused on the research, discovery and development of drugs to treat and prevent a variety of vascular diseases and conditions related to cancer and cancer treatments. Defibrotide, the Company's lead product candidate, is an investigational drug that has been granted Orphan Drug status by the U.S. Food and Drug Administration and EMEA to prevent and to treat VOD and Fast Track designation by the U.S. FDA for the treatment of severe VOD in recipients of stem cell transplants.

Cautionary Note Regarding Forward-Looking Statements

This press release contains "forward-looking statements." In some cases, you can identify these statements by forward-looking words such as "may," "might," "will," "should," "expect," "plan," "anticipate," "believe," "estimate," "predict," "potential" or "continue," the negative of these terms and other comparable terminology. These statements are not historical facts but instead represent the Company's belief regarding future results, many of which, by their nature, are inherently uncertain and outside the Company's control. It is possible that actual results, including with respect to the possibility of any future regulatory approval, may differ materially from those anticipated in these forward-looking statements. For a discussion of some of the risks and important factors that could affect future results, see the discussion in our Form 20F filed with the Securities and Exchange Commission under the caption "Risk Factors."

SOURCE: Gentium S.p.A.

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