

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**208114Orig1s000**

**MEDICAL REVIEW(S)**

## CONSULT FOR RARE PEDIATRIC DISEASE DETERMINATION

Date Submitted by Sponsor: 09/24/2015  
Date Received by FDA: 10/01/2015  
Date Received by Reviewer: 10/05/2015  
Date Review Completed: 03/18/2016  
Designation Number: 2015-5  
Trade name: Not determined  
Generic name (active ingredient): Defibrotide  
Sponsor: Gentium S.p.A  
US Resident Agent: Jazz Pharmaceuticals, Inc.  
Contact: Robin L. Hume, MS, RAC  
Director of Regulatory Affairs  
3180 Porter Drive  
Palo Alto, CA 94304  
Phone: 605.496.2901  
Email: [robin.hume@jazzpharma.com](mailto:robin.hume@jazzpharma.com)

### Regulatory Status:

The sponsor completed a rolling submission of NDA (#208114) on July 31, 2015, for the treatment of hepatic veno-occlusive disease (b) (4) dysfunction following hematopoietic stem cell transplantation. The NDA is being reviewed under priority review timeline with the PDUFA goal date of March 31, 2016. The sponsor has requested a Rare Pediatric Disease Voucher pursuant to FDASIA. OOPD has been consulted by CDER DHP to assist in assessing whether hepatic veno-occlusive disease (VOD) (b) (4) following hematopoietic stem cell transplantation (HSCT) is a rare pediatric disease. Defibrotide is currently only available to patients in the US through an ongoing expanded access treatment protocol. The drug has received fast-track designation for the treatment of severe hepatic VOD in HSCT and the European Commission granted marketing authorization for the drug for the treatment of severe hepatic VOD in HSCT therapy in those over one month of age.

Proposed Orphan Designation: Treatment of hepatic veno-occlusive disease (VOD) (b) (4) following hematopoietic stem-cell transplantation (HSCT)

**Orphan Drug Designation history:** Gentium S.p.A. holds orphan drug designation for defibrotide for both the prevention and treatment of hepatic VOD (see 06-2284 and 03-1688). Another company has been granted orphan drug designation for the drug for the treatment of thrombotic thrombocytopenic purpura.

### **Background of Disease or Condition**

Hepatic veno-occlusive disease (VOD) occurs most often following hematopoietic stem cell transplantation (HSCT) due to the myeloablative regimens that are used. However, the condition may also be due to exposure to chemotherapeutics (e.g., dacarbazine, oxaliplatin, 6-thioguanine) at more conventional doses as well as to chronic immunosuppression (e.g., azathioprine, 6-mercaptopurine). The condition may also occur in patients who receive chemotherapy and radiation to the abdominal areas (e.g., patients with Wilms tumor) as well as in those who are post hepatic transplantation.

The condition is the result of damage to sinusoidal endothelial cells and hepatocytes in the zone 3 of the hepatic acinus and typically is seen within 30 days post HSCT, although in some cases, it may not occur until 65 days post HSCT. The damage to the sinusoidal endothelial cells results in the obstruction of hepatic sinusoids. There is a migration of red blood cells, leukocytes and cellular debris into the space of Disse which is below the endothelial cells resulting in the dissection of the endothelial lining. Fibrin deposition and expression of factor VIII in venule walls occurs and is followed by necrosis of the perivenular hepatocytes. The sloughed sinusoidal lining embolizes and obstructs sinusoidal flow. Thickening of the subintimal zone leads to a narrowing of the venular lumen and increased resistance to blood flow which is implicated in post-sinusoidal portal hypertension, declining liver function, and ascites which all lead to multi-organ failure characterized by both pulmonary and renal failure and encephalopathy and eventually death.

Symptoms and signs of the disease include weight gain with or without ascites, right upper quadrant pain that is so severe that it may necessitate the use of narcotics, hepatomegaly and jaundice. In about 50% of patients with renal failure, hemodialysis is required. Patients may also suffer from thrombocytopenia which is resistant to platelet transfusions. The severity of VOD may range from mild disease to severe disease. Mild disease meets the diagnostic criteria for VOD but does not require treatment for excess fluid or medication for hepatic pain and has a self-limiting course with resolution seen within a few weeks. In moderate disease, there is a presence of liver injury requiring treatment for fluid excess or medication for hepatic pain, but this too, resolves completely. Severe disease is defined as VOD that leads to death or that does not resolve by day 100 post HSCT. Severe disease is usually defined by the presence of multi-organ failure and is associated with a high mortality rate. While this classification method exists, since the classification of severity depends on the clinical course, it is not helpful for guiding management of the disease in real time.

Diagnosis is made based on the clinical manifestations of VOD along with the presence of a risk factor for the development of the disease, such as HSCT and the exclusion of other similar diseases (e.g., cholestatic jaundice, drug-induced cholestasis, excess fluid due to renal failure or congestive heart failure, viral or fungal infections involving the liver in immunosuppressed individuals, graft-versus-host disease). While the gold standard for obtaining a confirmatory diagnosis is to measure the wedged hepatic venous pressure gradient, imaging studies can help to confirm the diagnosis. There are currently two sets of diagnostic criteria that are used for diagnosing VOD, the Seattle Criteria and Baltimore Criteria. The Seattle Criteria requires a patient to have two of the following three findings within 20 days of transplantation: 1) bilirubin >2 mg/dL; 2) hepatomegaly or right upper quadrant pain of liver origin; 3) >2% weight gain due to excess fluid accumulation. The Baltimore Criteria requires a patient to have hyperbilirubinemia >2 mg/dL plus at least two of the following: 1) hepatomegaly, usually painful; 2) ≥5% weight gain; 3) ascites.

Most patients see a gradual resolution of VOD 2-3 weeks after its onset. There are no currently available approved therapies to treat VOD. Treatment is symptomatic and should be initiated as soon as possible. Diuretics may be administered to help with the fluid overload seen with the disease and if they are ineffective, hemodialysis, paracentesis, and hemofiltration may need to be initiated. In patients with less advanced disease, the use of a transjugular intrahepatic portosystemic shunt may be an option and in those with severe disease, hepatic transplantation may need to be performed. Defibrotide, a polydeoxyribonucleotide with adenosine receptor agonist activity, has been used in the treatment of VOD. While not approved in the United States, the drug has been found to exert some effect on survival in VOD. While the precise mechanism of action for the drug remains unknown, the drug has demonstrated local antithrombotic, anti-ischemic and anti-inflammatory activity, thereby conferring protection to the endothelium. The drug works by protecting the endothelial cells and by restoring the thrombotic-fibrinolytic balance.<sup>1-4</sup>

### **Population Estimate**

#### *Incidence of VOD and VOD with evidence of MOD*

The incidence of VOD post HSCT varies from 10 to 60%. One study found a mean incidence of 13.7%. VOD with evidence of MOD following HSCT has occurred in about 20% of all VOD cases, however, the range for VOD with MOD has been reported to be between 0 and 77% of VOD cases. The Center for International Blood and Marrow Transplant Research (CIBMTR) data notes that there are about 20,000 transplants performed in the US annually. Applying the 13.7% mean VOD incidence as well as the 20% incidence of VOD with MOD, results in 2,740 HSCT patients per year who develop VOD and 548 HSCT patients per year who develop VOD with MOD. When using the highest reported VOD incidence of 60% as well as the highest reported VOD with MOD incidence of 77%, the figures are no more than 9,240 annually per the sponsor.

#### *Calculation demonstrating that VOD with MOD is a rare pediatric disease*

The sponsor notes that since the proposed indication they are seeking is for the treatment of hepatic VOD (b) (4) in patients who have undergone HSCT, the condition is

exclusive to only those undergoing transplantation. The sponsor uses four different data sets to demonstrate that VOD (b) (4) post HSCT is a rare pediatric disease:

1. CIBMTR registry of transplant patients
2. Experience from a US expanded-access study using defibrotide
3. Data from a health economics and outcomes study
4. Guidelines on pediatric indications for HSCT

#### CIBMTR registry of transplant patients

- Pediatric patients are at higher risk for developing VOD with MOD post HSCT compared to adult patients
- The CIBMTR database performs prospective, and observational research using a large network of transplant centers and a database of more than 330,000 transplant patients. Outcomes data is collected on every allogeneic transplantation performed in the US and about 94% of VOD with MOD cases develop after allogeneic transplantation. Autologous transplantation data is voluntarily submitted and CIBMTR captures about 80% of these types of transplantations.
- CIBMTR developed a weighted-randomization selection algorithm that determines the forms needed for each transplant recipient (transplant-essential data) with a sample of sites also receiving full detailed case report forms. The algorithm randomly selects around 20% of recipients for whom a case report form is to be requested. It gives higher weights to patients receiving a transplant for a rare condition, to very young and old patients, and to novel treatments. For those who consent to participate, the algorithm determines the transplant follow-up data submission level (e.g., transplant-essential data w/o w/o the case report form) and for those who do not consent to participate, the algorithm is not used and follow-up data must be submitted on a transplant-essential data form.
- Data showed the risk of developing VOD with MOD of 0.045 (148/3,316) for pediatric HSCT patients versus 0.011 (172/16,030) for adults.
- The sponsor concludes that the risk of developing this condition is higher in pediatric patients versus adult HSCT patients

#### Experience from a US expanded-access study using defibrotide

- Study included patients from 78 geographically diverse medical centers in the US
- Study was initiated in 2007 and used a data cutoff for NDA of December 5, 2014
- At time of data cutoff, 53.8% (189/351 patients) had VOD with MOD and were 16 years of age or younger
- The sponsor concludes that this is further support that pediatric patients are at greater risk for VOD with MOD post HSCT

#### Data from a health economics and outcomes study

- This study used the Premier Research Database and was a retrospective, observational study to examine healthcare utilization and costs associated with VOD with MOD and to also describe the characteristics of VOD with MOD

- Database contains one in every five patient discharges throughout the US and included patients with inpatient HSCT procedure who were discharged between January 1, 2009 and May 31, 2014
- Relied upon coding algorithm to identify HSCT patients with VOD as well as the subset who go on to develop VOD with MOD
- Total population was 5,418 with 291 or 5.4% of patients with VOD and 134 patients or 2.5% with VOD with MOD
- Incidence of VOD with MOD in pediatric patients up to 17 years of age is 4.2% (20 per 471 transplants) versus 2.3% (114 per 4,947 transplants) for those 18 years of age and older
- The sponsor concludes that the risk for developing VOD with MOD is higher in pediatric patients versus adults

#### Guidelines on pediatric indications for HSCT

- Various pediatric or primarily pediatric diseases are indicated for HSCT
- Sponsor notes that at least 33% of HSCTs are done for rare indications including infant and childhood acute myeloid leukemia and osteopetrosis
- Corbacioglu reported 63.6% incidence of VOD and 27% incidence of VOD with MOD in pediatric patients after HSCT who suffered from malignant infantile osteopetrosis
- Disease for which HSCT is recommended include: severe combined immunodeficiency, osteopetrosis, juvenile myelomonocytic leukemia, Wiskott-Aldrich syndrome, high-risk pediatric disease subgroups such as infant/childhood acute myeloid leukemia, infant or childhood acute lymphoblastic leukemia, and childhood myelodysplastic syndromes
- The sponsor concludes that since pediatric conditions are predominantly indicated for HSCT, they present a risk to pediatric patients of developing VOD following HSCT

#### Conclusion

- Cedaro et al found that age less than 7 years is an independent risk factor for VOD and Bajwa found that infants less than 6 months of age are at high risk of developing severe VOD
- The sponsor believes that all of the above information when taken together supports that VOD with MOD following HSCT is a rare pediatric disease
- The sponsor does note that pediatric patients demonstrate better survival outcomes even though they are at a higher risk for VOD with MOD than adults

#### REVIEWER'S COMMENTS:

##### Demonstrating that hepatic VOD is a rare disease

*While hepatic VOD can have various etiologies other than just HSCT, HSCT is the most common cause of hepatic VOD. Taking 60% (highest incidence of VOD in HSCT) of 20,000 (annual number of HSCT performed) results in an incidence of VOD of 12,000. Even if one were to assume that all HSCT recipients developed VOD, the incidence of the disease is well under 200,000. The use of incidence appears to be appropriate in that the*

*disease appears to be acute in nature. In the designation request for the treatment of hepatic VOD (see 03-1688), incidence was used as a measure of prevalence.*

**Demonstrating that hepatic VOD is a rare pediatric disease**

*While there is no doubt that hepatic VOD is an orphan disease, the issue with this application concerns the sponsor's target population. The sponsor wants to restrict the use of their product to those with VOD (b) (4) following HSCT. There is no justification provided to support restricting the use of defibrotide to this subset of VOD patients. The sponsor's desire to restrict their marketing indication to a particular population is not sufficient justification to restrict the rare pediatric disease designation indication also to that narrow population. The OOPD designates a product for a disease or condition and in this case, it would appear that the disease at hand is hepatic VOD (b) (4) following HSCT. Unless there is some feature of the product that would preclude its use in all patients with hepatic VOD, the rare pediatric disease population estimate should take into consideration all patients with hepatic VOD. In order to qualify for rare pediatric disease designation, the sponsor must demonstrate that >50% of the incident cases of hepatic VOD occur in those 0 through 18 years of age. An Emedicine paper notes that the incidence of VOD ranges from 5-60% in children and that similar rates have been reported in adults.<sup>5</sup>*

**New Information Request from OOPD to Sponsor**

The sponsor was notified of the deficiencies in their population estimate calculation and was asked to respond to these deficiencies in an email communication.

**Sponsor Response to Information Request from OOPD (11/20/2015)**

**The reason why hepatic VOD (b) (4) post-HSCT was chosen:** This was done to capture the population with a positive benefit/risk profile with defibrotide and highest mortality risk when left untreated. The pathology of VOD that the drug treats is one that occurs with certain regimens including pre-HSCT therapy and chemotherapy/radiation outside HSCT. Therefore, the drug would be limited to regimen-related hepatic VOD and would not be used in chronic immunosuppression or post-liver transplantation. No pharmacodynamics or clinical data exists to support efficacy in these settings. A VOD risk factor that is specific to the transplant procedure is alloreactivity that contributes to endothelium damage and VOD pathophysiology, with the risk of developing VOD being higher when alloreactivity is higher (e.g., after allogeneic transplant, with unrelated donors and HLA-mismatched donors, non-T cell depleted allogeneic transplantation).

**Methodology for recalculating the population estimate**

1. Include the entire hepatic VOD population:
  - a. Incidence of hepatic VOD in HSCT setting from original request based on CIBMTR data and literature
  - b. Literature on VOD outside of the HSCT setting
  - c. Data from the Sponsor's expanded-access Study 2006-05 which the sponsor states parallels figures in the literature on VOD which further supports the accuracy of the study in reflecting entire hepatic VOD population for the below reasons:

- i. Includes both VOD with or without MOD and following HSCT or chemotherapy
  - ii. Study is only way patients in the US have access to defibrotide; provides drug at 95 of the 189 US centers where patients with VOD are likely to be treated; Data represents 867 patients over 7 years
  - iii. Study is being conducted at FDA's request to obtain safety information about the drug in the population most likely to receive the marketed product upon approval
    - a. Incidence of hepatic VOD in adults and pediatrics in HSCT and chemotherapy setting reflects real world incidence of hepatic VOD and is a strong predictor of the population that is likely to use the product in and outside of the HSCT setting
2. Study was also initiated in response to large numbers of emergency use IND requests for the drug
    - a. Study was expanded to include patients with late onset VOD, all severities of the disease, those who develop the disease after chemotherapy or HSCT
    - b. HSCT and chemotherapy induced VOD in the literature constitutes the majority of VOD cases with regimens for HSCT being the main cause of the condition
  3. Study includes VOD cases based on both Seattle criteria and Baltimore criteria
  4. Study includes post-chemotherapy patients with same underlying diseases that are described as being associated with VOD outside of HSCT
  5. Small numbers of post-chemotherapy patients included in the study is consistent with small proportion of hepatic VOD occurring outside of HSCT
  6. Incidence of hepatic VOD versus hepatic VOD with MOD in the study are consistent with CIBMTR data and show that about 50% of hepatic VOD develop into VOD with MOD

### Calculation

#### *1. Hepatic VOD in post-HSCT Population*

- Highest incidence of hepatic VOD in this population
- 91% of hepatic VOD cases from Study 2006-05 occurred in this population with remaining 9% occurring in those post-chemotherapy (Wilms tumor, neuroblastoma, rhabdomyosarcoma, acute lymphocytic and acute myeloid leukemias [ALL, AML])
- In Study 2006-05, 61% were younger than 18 years of age and 38.9% were  $\geq 18$  years of age

- Incidence of hepatic VOD post-HSCT from literature:
  - Sponsor provides various estimates from 6.5% to 17.3% but chooses to use a mean incidence from the Coppel et al paper of 13.7%
  - Provides another incidence of 60% also from the Coppel review
- CIBMTR data notes that there are 20,000 transplants done each year. Using 13.7% and 60% figures above results in **2,740 and 12,000 cases of hepatic VOD post-HSCT per year**, respectively
- Sponsor notes that hepatic VOD with or without MOD is 5 times the VOD with MOD population and 1.3 times the highest upper range estimate of the 60% incidence of VOD post-HSCT
- Data from Study 2006-05 and CIBMTR fall within this range per sponsor
  - Study 2006-05 data notes that 56% of post-HSCT patients develop VOD with MOD
  - CIBMTR data show that 48% of hepatic VOD patients have VOD with MOD
- Data from Study 2006-05 show a higher proportion of pediatric (<18 years) versus adult patients ( $\geq 18$  years) with hepatic VOD post-HSCT (61.1% vs 38.9%, respectively)
- Paper by Corbacioglu describes higher incidence of hepatic VOD post-HSCT in children (mean incidence of 25% vs 13.7% in adults)

## 2. *Hepatic VOD outside of HSCT Population*

- Chemotherapy has been associated with development of hepatic VOD
  - DeLeve 2008 paper notes that hepatic VOD develops sporadically in those who receive other forms of chemotherapy outside of myeloablative regimens for HSCT
  - Dahl & Girault note that hepatic VOD rarely develops after exposure to hepatotoxic chemotherapies outside those used in HSCT
  - Richardson et al 2012 paper notes that 5.4% of their population developed hepatic VOD following chemotherapy alone
  - Cefalo et al 2010 notes that hepatic VOD due to conventional chemotherapy is usually less severe and is slower to be fatal than hepatic VOD post-HSCT
  - Data from Study 2006-05 notes only 9% of patients post-chemotherapy developed hepatic VOD and sponsor notes this is consistent with the lower incidence of hepatic VOD outside HSCT setting found in the literature
  - Study 2006-05 data shows that the post-chemotherapy hepatic VOD population also includes higher proportion of pediatric patients than adults (79.7% versus 20.3%); 79.7% figure is based on those who are  $\leq 16$  years of age, not  $\leq 18$  years of age.
- *Literature for Hepatic VOD outside of HSCT Population*
    - Sponsor notes that hepatic VOD due to Wilms tumor, neuroblastoma, and rhabdomyosarcoma most often occurs with HSCT but has also been

reported in patients after receiving chemotherapy outside HSCT; sponsor notes that these malignancies are rare and occur almost exclusively in pediatric patients

○ 1. Wilms Tumor

- American Cancer Society says that Wilms tumor occurs primarily in first 5 years of life with about 3% of cases occurring in adults per a paper by Huszno et al 2013; American Cancer Society estimates incidence of 500 cases per year
- Czauderna et al 2000 documented 10 cases of hepatic VOD out of 206 children with Wilms tumor and note that a 5% occurrence of VOD in their study is similar to other reports
- Using 500 incidence rate and 5% occurrence of hepatic VOD in those with Wilms tumor, sponsor estimates 25 cases of hepatic VOD due to Wilms tumor

○ 2. Neuroblastoma

- Smith et al 2013 notes that the condition is rare in adults; American Cancer Society notes that condition is extremely rare in adults
- American Cancer society notes incidence of 700
- Franks et al 1997 notes that less than 10% of cases occur in those older than 10 years of age
- Matthay et al 1999 paper notes that of 539 patients with neuroblastoma, 9% of the 189 patient assigned to HSCT developed VOD and 0% of the 150 patient assigned to chemotherapy alone developed the disease
- Sponsor notes that they were unable to find reports of neuroblastoma outside of the HSCT setting noting that this may be due to the fact that most cases progress to HSCT

○ 3. Rhabdomyosarcoma

- American Cancer Society notes that 3% of all childhood cancers are rhabdomyosarcomas with an incidence of 350 cases per year
- Sultan et al 2009 notes the condition is extremely rare in adults
- Ortega et al 1997 notes that hepatic VOD in this population occurred in 1.2% of children
- Using the American Cancer Society incidence and the 1.2% incidence rate of hepatic VOD in this population results in 4 cases of hepatic VOD due to rhabdomyosarcoma

- 4. ALL and AML
  - American Cancer Society incidence for AML is 20,830 and notes it occurs primarily in adults
  - American Cancer Society incidence for ALL is 6,250 with about 40% of cases occurring in adults
  - Richardson et al 2012 study notes that AML and ALL were common underlying diseases in 61 patients who developed VOD post-chemotherapy alone, representing 1.6% and 1.9%, respectively of the total VOD non-HSCT population
  - There are many case reports of single individuals developing the disease post-chemotherapy
  - Sung et al 2010 notes 1% of patients with de novo AML developed VOD post-chemotherapy
  - Vora et al 2006 notes that 6.3% children developed VOD post-chemotherapy
  - Using American Cancer Society incidence of 20,830 cases of AML and the 1.3% incidence of VOD outside HSCT setting (averaged 1.6% and 1% rates from two studies that included adults and pediatric patients), sponsor estimates 270 cases of VOD in AML patients
  - Using American Cancer Society incidence of 6,250 cases of ALL and the 1.9% incidence of VOD (Richardson et al 2002), sponsor estimates 119 cases of VOD in ALL patients
  
- 5. VOD due to Immunosuppressive Regimens, Renal Transplant, or Liver Irradiation
  - Sponsor notes that they only found anecdotal, limited individual patient reports
  - Weitz et al 1982 notes in four patients on immunosuppressive therapy for chronic iridocyclitis or post renal transplantation, hepatic VOD was documented
  - Marubbio & Danielson 1975 notes one case of VOD post immunosuppressive treatment following renal transplantation
  - Various papers report VOD and VOD-like lesions post irradiation of the liver
  - Sponsor notes that it is unclear if VOD secondary to immunosuppressive therapy, liver irradiation, or renal transplantation involves a similar mechanism to VOD following myeloablative or chemotherapy regimens
  
- In totality, sponsor notes that VOD outside of HSCT is rare with only 418 cases reported

- Proportion of pediatric hepatic VOD not due to HSCT cannot be determined due to the limited cases identified but sponsor notes that four of the five diseases in which hepatic VOD is reported outside the HSCT setting are primarily pediatric diseases

#### Incidence of VOD in pediatric patients

- Sponsor states that in their Study 2006-05, there were 61.1% pediatric patients post-HSCT and 79.7% pediatric patients post-chemotherapy (aged  $\leq 16$  years). This with the higher risk of developing VOD in pediatric patients undergoing transplant of 0.092 versus 0.022 in adults, and the fact that VOD not due to HSCT has been mainly reported in rare pediatric diseases, support that their proportions accurately reflect the entire hepatic VOD population.
- Sponsor uses the proportions of pediatric patients from their Study 2006-05 and applies this to the entire VOD population (12,000 HSCT post-VOD and 418 post-chemotherapy VOD) to yield a total pediatric population of 7,665. They conclude that >50% of the VOD population is aged under 18 years (7,665 pediatric vs 12,418 total).

#### New Information from CDER Rare Diseases Program

Dr. Johnathan Goldsmith informed OOPD that the CIBMTR reports from 2013 noted that there were a total of 19,220 transplants conducted of which 2,408 were under 21 years of age and 16,812 were 21 years of age and older. He noted that if one applies the percentages noted in a paper by Coppell et al (13.7% mean incidence of VOD across all age groups) and Corbacioglu et al (25% mean incidence of VOD in children), there would be 2,031 adults who develop VOD in a year vs 602 children. This would not make hepatic VOD a rare pediatric disease.

#### New Information Request from OOPD to Sponsor

An email was sent to the sponsor on 3/4/2016 with the figures derived from the CIBMTR data. The sponsor was asked to dispute the figures if they disagreed. The email also asked the sponsor to provide the breakdown for the number of patients with VOD for 2014 (n=66) who were <19 years of age and  $\geq 19$  years of age from the table in Appendix 2 of their application which presented data from CIBMTR on the number of VOD cases from 2008-2014.

Given that CIBMTR collects registry and research level data and given that the VOD figures are from the research level data, the sponsor was also asked to answer how the research level data from CIBMTR would represent all cases of VOD or even the majority of cases of VOD in the US especially if only 25% of patient records are assigned to this research level data and how it is representative of the larger registry population. They were also asked to comment on why the figures provided to this reviewer from CIBMTR for the 2014 hepatic VOD population were different from the figures they provide in their Appendix 2.

**Sponsor Response to Information Request from OOPD (3/11/2016 and 3/14/2016)**  
**Limitations to the CDER Calculations and why CIBMTR and Study 2006-05 are more Relevant Sources for Data on Hepatic VOD**

The sponsor disagrees with using the 25% mean VOD incidence in pediatric patients from the Corbacioglu (2012) paper. The sponsor provides what they consider to be the most current data regarding VOD incidence in the US population. Based on these data, pediatric patients have a fourfold higher incidence of VOD compared to adults, using either cumulative (2008-2014) or most recent (2014) US data from CIBMTR. They note that the Corbacioglu et al. (2012) paper provides a mean incidence of VOD following transplant and that the incidences in children ranged from 11% to 60%. They note that the studies included were primarily ex-US studies. The sponsor cites some risk factors documented in the article for developing hepatic VOD: younger age (children younger than 6.7 years), which was associated with an increased incidence of VOD compared with that in children ages 6.7 years and older; increased incidence due to certain malignant and inherited diseases that are associated with a substantially increased risk of VOD during SCT including neuroblastoma..., familial hemophagocytic lymphohistiocytosis (Griscelli syndrome)... and osteopetrosis..., in addition to prior hepatic disease, such as HCV infection..., fibrosis or cirrhosis...”.

They note that a subanalysis of the data from Coppel’s review of VOD incidence (2010) demonstrated that the inclusion of older studies with more intensive conditioning regimens may have led to the higher (13.7%) rate of VOD found in that review (Tsirigotis et al. 2014). In a more recent study, in which 271 patients received reduced-intensity conditioning for allogeneic HSCT, the cumulative incidence of VOD in patients with hematologic malignancies was 8.8%. A paper by Carreras et al. (2011) found that the intensity of the conditioning regimen was the most predictable variable for increased incidence of VOD, with 8% and 2% incidences of VOD following myeloablative and reduced-intensity conditioning, respectively. They note that there is a large amount of data that shows that the incidence of VOD has decreased over time with the increasing use of reduced-intensity conditioning regimens.

The sponsor suggests that the Agency’s evaluation should equally consider the two sources of data that they believe are more recent than those reviewed by Coppel (studies from 1979-2007) and Corbacioglu (2002-2010) since these data use more consistent methodology than the wide range of studies in the Coppel and Corbacioglu reviews: 1) the incidence and relative risk of VOD in pediatric and adult populations based on 2014 CIBMTR data, which are from a sufficiently large population to provide a reliable incidence rate, and 2) data from a real-world patient population with VOD from expanded-use study 2006-05.

The risk of developing VOD following HSCT in pediatric and adult patients shows that pediatric patients have a more than fourfold higher risk of developing VOD following HSCT compared to adults (9.2% vs 2.2%). This is based on CIBMTR data (Appendix 2) for the period from 2008 to 2014 and used the following calculations:

Pediatric patients with VOD/total number of pediatric transplants from 2008-2014 =  $156 + 148/3316 = 304/3316 = 9.2\%$ .

Adult patients with VOD/ total number of adult transplants from 2008-2014 =  $153 + 134 + 15 + 23 + 19 + 15/10,182 + 2,595 + 3,253 = 359/16,030 = 2.2\%$

In the expanded-access Study 2006-05, 61.1% of patients with VOD were younger than 18 years of age which the sponsor notes is consistent with findings in the literature suggesting that younger children (11 years of age or younger) comprise the pediatric subgroup with the highest incidence of VOD.

The sponsor believes that the Study 2006-05 data provide an accurate reflection of the US VOD patient population and serve as a strong predictor of the population affected by VOD. The study is being conducted at FDA's request to collect safety information about defibrotide use in an expanded patient population to represent the population most likely to receive defibrotide for treatment of VOD following product approval. The study uses the well-accepted Baltimore and Seattle criteria for VOD, which were used in several comprehensive reviews of VOD incidence as well as in multiple individual studies of VOD, and patients are exposed to the same types of conditioning regimens described as associated with VOD in the literature. They believe the inclusiveness of expanded-use Study 2006-05 and the parallels between the data from this study and those in the published literature on VOD support the ability of the study in estimating VOD incidence in the US. They state that the recent data generated in a real-world patient population, support the conclusion that hepatic VOD is a rare pediatric disease. They also believe that the demonstrated higher risk of developing VOD among pediatric patients meets the definition of a rare pediatric disease in showing that the disease "primarily affects individuals aged from birth to 18 years, including age groups often called neonates, infants, children, and adolescents."

The 2014 CIBMTR data showing age subgroups for the 66 patients with VOD are as follows:

<b>Year 2014</b>	<b>Non- severe VOD</b>	<b>Severe VOD</b>	<b>Number of Transplant</b>
<19 years of age	13	15	460
≥19 years of age	24	14	2,437

They note that the overall incidence of VOD following transplant is 2.3%, which is consistent with the finding that the incidence of VOD has been decreasing in recent years with use of reduced intensity conditioning regimens (Tsirigotis et al. 2014, Carreras et al. 2011). Using the 2014 CIBMTR totals by age group for patients with VOD and for numbers of transplants, they calculate the most recent risk of VOD following HSCT for pediatric and adult patients:

Pediatric patients:  $13 + 15/460 = 6.1\%$

Adult patients:  $24 + 14/2,437 = 1.56\%$

The CIBMTR 2014 data show that pediatric patients have approximately a fourfold increased risk of developing VOD following HSCT compared to adults. This higher risk in pediatric patients is consistent with the greater risk demonstrated using CIBMTR data from 2008 to 2014.

#### CIBMTR Data Collection Process

The sponsor contracts with the CIBMTR for data and analyses of the US transplant population. CIBMTR is a research collaboration between the National Marrow Donor Program/Be The Match and the Medical College of Wisconsin. CIBMTR performs prospective and observational research based on a broad network of transplant centers and a clinical database of more than 330,000 transplant recipients. CIBMTR collects outcomes data on every allogeneic transplantation performed in the US, as required by law. Approximately 94% of VOD cases develop after allogeneic transplants. Transplant centers in the US also voluntarily submit autologous transplantation data; CIBMTR estimates that its database has captured approximately 80% of autologous transplants.

Data is collected on the TED and CRF (research) levels. The TED data set is an internationally accepted standard data set that contains a limited number of key variables and is required for all consecutive transplant recipients. The CRF data set captures additional patient, disease and treatment-related data. Approximately 25% of patient records are assigned to CRF level data collection and are selected to be a representative sample of the larger TED population. The CIBMTR collects information specific to VOD at the CRF level only (Appendix 2 VOD data is limited to this group). CIBMTR data on numbers of transplants and numbers of patients with VOD in the US yield an overall incidence of VOD following transplant of 2.3%.

CIBMTR is an independent organization that maintains the largest observational database of clinical information on HSCT in the US. Its research data set was designed to provide representative, adequately sized subsets of patients for studies requiring detailed data. This research data set can be considered representative of the overall CIBMTR registry. About two-thirds of the more than 400 transplant centers throughout the US that provide data to CIBMTR submit CRF data for a subset of their patients, representing the majority of the registry's centers (CIBMTR Progress Report 2013). Further, the weighted-randomization selection algorithm used to select cases for CRF submission is designed to **randomly** select a sample of recipients for whom a CRF will be requested, minimizing the potential for bias. Although no subset can be identical to the whole, the CIBMTR research data set provides a randomized, representative sample of the CIBMTR registry.

As with all approaches to estimating patient populations, the CIBMTR data represent an approximation of the total US patient population with hepatic VOD. The sponsor believes that CIBMTR provides the best and most representative data available for estimating the incidence of VOD in pediatric and adult patients in the US. In contrast to the literature, which relies on primarily ex-US studies, CIBMTR are recent and are specific to the US. In addition, the CIBMTR data were collected using a consistent, prospectively defined approach, whereas the multiple studies analyzed in the literature incorporated a variety of approaches and diagnostic criteria.

## Conclusion

Data from CIBMTR, which collects data on 100% of allogeneic transplants and 80% of autologous transplants in the US, showed that pediatric patients have a higher incidence of hepatic VOD following transplant compared to adults. For the period 2008 to 2014, CIBMTR data show incidences of hepatic VOD of 9.2% and 2.2% for pediatric and adult patients, respectively. For the year 2014, CIBMTR data show incidences of 6.1% and 1.56% for pediatric and adult patients, respectively. The sponsor believes that this higher incidence of hepatic VOD for pediatric patients meets the definition of a rare pediatric disease in showing that this rare disease “primarily affects individuals aged from birth to 18 years, including age groups often called neonates, infants, children, and adolescents.” This is further supported by the data from study 2006-05, which showed that more than 50% of patients with hepatic VOD in the US are younger than 18 years of age.

Despite the limitations of the CIBMTR database, the sponsor notes that their estimation that the fourfold greater risk for pediatric versus adult patients with VOD demonstrated in CIBMTR data for 2014 (and for the period 2008-2014) would meet the greater than 50% criterion even when the CIBMTR weighted-randomization algorithm and the subpopulation of research data are considered. Further, the higher incidence of VOD in pediatric patients reflected in the CIBMTR data is consistent with data from Study 2006-05, in which 61% of an expanded-access study population were younger than 18 years. Taken together, we believe these data demonstrate that VOD meets the criteria for a rare pediatric disease.

## Reason for Discrepancy between CIBMTR Data provided to FDA and Sponsor’s Appendix 2 Data

In response to our question about the 2014 data provided to us and to FDA, Patricia Steinert of CIBMTR responded: “We compared the data that was provided in the table to Jazz and the data that was recently requested by the FDA via our info-request email. The Jazz data uses a data retrieval dated June 2015 (we retrieve CRF level data quarterly), the FDA data used a December 2015 retrieval. As we are a registry, we receive data on an ongoing basis and we routinely see a 6-9 month lag in its receipt. The increase in reported numbers are not outside of a range that we would expect to see in this timeframe.”

## REVIEWER’S COMMENTS:

### Use of Corbacioglu and Coppel Papers to Determine Proportion of Pediatric and Adult Hepatic VOD Patients Per Year

*The use of the 25% (pediatric) and 13.7% (all ages) mean incidence of VOD estimates from the Hepatic VOD after HSCT publication (Dalle et al Biol Blood Marrow Transplant 2016; 22:400-409) is not accurate as there are several limitations to using these incidence rates and applying them to the pediatric HSCT (25% rate) and total HSCT populations (13.7%) respectively. The 25% rate is from the Corbacioglu paper while the 13.7% rate is from the Coppel paper. The limitations of these figures are noted below.*

### *Corbacioglu*

- *Studies used for incidence include ex-US studies so the generalizability to the US population is unclear*
- *Studies use different criteria (Baltimore [more restrictive] or Seattle) to determine VOD cases*
- *Study averages the incidences of several studies that use different criteria, perhaps different data collection methodologies, patient populations with different risk factors etc which can all affect figures for VOD making the accuracy of the 25% incidence figure questionable*

### *Coppell*

- *Uses 135 studies to calculate an average incidence of VOD of 13.7%*
- *Studies again used differing criteria for diagnosing VOD*
- *Authors note differences in the incidence of VOD in the studies queried are due to the diagnostic criteria used (Seattle vs Baltimore), study design, endpoints, data reporting methods with many studies relying on retrospective data that could be flawed since it is dependent on accuracy and extent of documentation; patients with different risk factors for VOD, different conditioning regimens used (high intensity has been associated with higher incidence of VOD than reduced intensity regimens), patient selection, primary disease as well as other co-morbidities, presence of pre-existing risk factors for liver toxicity*
- *Data in this study was not stratified according to these multiple variables and is noted as a limitation of the study*

### *Pros and Cons of Using CIBMTR Data and Sponsor Study Data*

*It would seem that using the data from the sponsor's study as well as the CIBMTR data would be more accurate than using the incidences provided from the above studies since the data are more recent and pertain to the US population. But there are limitations to these sources of data as well.*

### *CIBMTR*

- *It appears that the main limitation with the CIBMTR is that not all patients who undergo HSCT are taken into consideration when determining the number that suffer from VOD. The determination of the number of patients with VOD is made on a subregistry level and not on the registry level. This reviewer outreached to Biostatistician Xiaochun Zhu who noted the following "The CIBMTR adjusts percentage of patients/diseases selected from registry for research. The number may change each year. Therefore if you use number from CIBMTR research level to estimate all US center it is not accurate."*
- *According to Patricia Steinert, CIBMTR Administrator, "CIBMTR collects data at two levels; the Transplant Essential Data (TED) level is an internationally accepted standard that contains a limited number of key variables and is collected for all consecutive transplant recipients; we collect close to 100% of allogeneic and an estimated 80% of autologous US transplants. The Comprehensive Report Form (CRF) captures additional patient, disease and treatment-related data. We use a selection algorithm to place a patient record on the CRF reporting track.*

*Only patients from centers that agree to this level of reporting are eligible for CRF selection and, because we pay for these forms, our ability to collect may change from year to year. We feel the selection algorithm provides diversity in the CRF population and we consider it a representative sample of the overall database. However, this consideration is appropriate at a high level, e.g. disease, transplant type, donor, etc. CRF may not be representative of smaller, event based, populations. The VOD event is captured only on the CRF forms. Therefore, it is difficult to generalize using actual numbers to the entire US population.”*

#### **Sponsor Study**

- *Found that 61.1% of patients with VOD were younger than 18 years of age and that similar to what is noted in the literature (Corbacioglu et al paper), younger children (11 years of age or younger) comprise the pediatric subgroup with the highest incidence of VOD.*
- *Study is being conducted at FDA’s request to obtain safety information about the drug in the population most likely to receive the marketed product upon approval*
- *Uses Baltimore and Seattle criteria for defining hepatic VOD (Coppell et al paper notes that Seattle criteria were quoted more in the literature for defining incidence of VOD)*
- *Study included patients from 78 geographically diverse medical centers in the US*
- *Study is only way patients in the US have access to defibrotide; provides drug at 95 of the 189 US centers where patients with VOD are likely to be treated; Data represents 867 patients over 7 years*
- *Study includes post-chemotherapy patients with same underlying diseases that are described as being associated with VOD outside of HSCT*
- *Study was expanded to include patients with late onset VOD, all severities of the disease, those who develop the disease after chemotherapy or HSCT*
- *Includes both VOD with or without MOD and following HSCT or chemotherapy*
- *HSCT and chemotherapy induced VOD in the literature constitutes the majority of VOD cases with regimens for HSCT being the main cause of the condition*
- *Study includes VOD cases based on modified Seattle criteria, Baltimore criteria, or biopsy (sponsor email correspondence on 3/15/2016)*

*There are many limitations with the published studies as noted above and this would apply to the sponsor’s study as well as to the CIBMTR data. To justify that hepatic VOD is a rare pediatric disease, out of the entire incidence of hepatic VOD, greater than 50% should consist of those under 19 years of age. While the sponsor notes that the higher risk of developing VOD among pediatric patients meets the definition of a rare pediatric disease, it is not the rate of risk that matters, rather it is breakdown of the pediatric and adult populations from the total incidence of hepatic VOD that matters. It is just not possible, given the disproportionate number of adults who undergo HSCT in a given year compared to the proportion of children who undergo HSCT per year, to justify that hepatic VOD is a rare pediatric disease. The incidence of hepatic VOD in pediatric patients would have to be many fold higher than in adults for the numbers to work.*

### **Scientific Rationale**

The efficacy and safety of defibrotide in patients with VOD with MOD post HSCT have been assessed in one pivotal study and two supportive studies. The pivotal study was a Phase 3, multicenter, open-label, historical control study. The supportive studies included an investigator-initiated Phase 2 randomized, open-label study and another open-label expanded-access study. All studies enrolled both adults and children. The primary - efficacy endpoint in the pivotal study was survival at Day+100 post HSCT and the secondary endpoint was a complete response by Day+100. The results from the pivotal study found that the differences at Day+100 in survival and complete response rates were 23% and 19% for defibrotide versus historical controls, respectively. When data from the three studies were pooled, there was evidence of a consistent improvement in survival at Day+100 compared to patients who received no treatment. Data from the CIBMTR database was compared to the study outcomes noted above. The sponsor notes that the rates for Day+100 survival and VOD resolution after HSCT were 39% and 51.2% for defibrotide and 30.9% and 29.1% for patients not treated with defibrotide.

The sponsor notes that in their studies, pediatric patients had higher survival rates when compared to adults. They note that at Day+100 there were 51.4% pediatric patients versus 36.6% adult patients who were alive.

### **REVIEWER'S COMMENTS:**

*There is sufficient scientific rationale presented.*

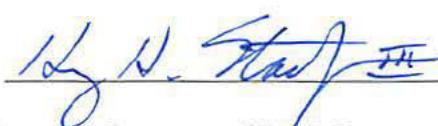
### **Evaluation and Recommendations**

The sponsor is requesting a Rare Pediatric Disease Voucher for defibrotide for the treatment of hepatic veno-occlusive disease (VOD) (b) (4) following hematopoietic stem-cell transplantation (HSCT). After further communication with the sponsor, the disease has been broadened to include all

hepatic veno-occlusive disease (VOD). However, the information presented is not supportive of the fact that hepatic veno-occlusive disease is a rare pediatric disease.



Soumya Patel, Pharm.D.  
Health Science Administrator

Concur:  Date: 3/24/2016

Henry H. Startzman III, M.D.  
Director, Orphan Drug Designation Program  
Office of Orphan Products Development

Cc:  
HF-35 / Designation File # 2015-5  
HF-35 / Chron File  
HF-35 / Soumya Patel

- 
1. Mohty M, Malard F, Abecassis M et al. Sinusoidal obstruction syndrome/veno-occlusive disease: current situation and perspectives – a position statement from the European Society for Blood and Marrow Transplantation (EBMT). *Bone Marrow Transplantation* 2015; 50:781-89.
  2. DeLeve LD, Valla DC, Garcia-Tsao G. Vascular disorders of the liver. [https://www.aasld.org/sites/default/files/guideline\\_documents/VascularDisordersLiver2009.pdf](https://www.aasld.org/sites/default/files/guideline_documents/VascularDisordersLiver2009.pdf)
  3. Kumar S, DeLeve LD, Kamath PS et al. Hepatic veno-occlusive disease (sinusoidal obstruction syndrome) after hematopoietic stem cell transplantation. *May Clin Proc* 2003; 78:589-98.
  4. Orphanet. Hepatic veno-occlusive disease. [http://www.orpha.net/consor/cgi-bin/OC\\_Exp.php?Lng=EN&Expert=890](http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=890)
  5. Harper JL, Arceci RJ. Veno-occlusive hepatic disease. [emedicine.medscape.com/article/989167-overview#a6](http://emedicine.medscape.com/article/989167-overview#a6)
  6. Pasquini MC, Zhu X. Current uses and outcomes of hematopoietic stem cell transplantation: 2014 CIBMTR Summary Slides.
  7. Orphanet. [http://www.orpha.net/consor/cgi-bin/OC\\_Exp.php?Lng=EN&Expert=890](http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=890)
  8. Bisogno G, de Kraker J, Weirich A et al. Veno-occlusive disease of the liver in children treated for Wilms tumor. *Medical and Pediatric Oncology* 1997; 29:245-51.
  9. American Cancer Society. Wilms tumor. <http://www.cancer.org/cancer/wilmstumor/detailedguide/wilms-tumor-key-statistics>.
  10. American Cancer Society. Neuroblastoma. <http://www.cancer.org/cancer/neuroblastoma/detailedguide/neuroblastoma-key-statistics>.

11. American Cancer Society. Rhabdomyosarcoma.  
<http://www.cancer.org/cancer/rhabdomyosarcoma/detailedguide/rhabdomyosarcoma-key-statistics>.
12. American Cancer Society. Acute myeloid leukemia.  
<http://www.cancer.org/cancer/leukemia-acute-myeloidaml/detailedguide/leukemia-acute-myeloid-myelogenous-key-statistics> .
13. American Cancer Society. Acute lymphocytic leukemia.  
<http://www.cancer.org/cancer/leukemia-acute-lymphocyticallinadults/detailedguide/leukemia-acute-lymphocytic-key-statistics>.
14. Jalandhara N, Thakor P, Goswami M et al. Hepatic veno-occlusive disease in a kidney transplant patient: case report and review of the literature. *Dialysis & Transplantation* 2011; 40:226-230.
15. Sebah M, Debette M, Samuel D et al. “Silent” presentation of veno-occlusive disease after liver transplantation as part of the process of cellular rejection with endothelial predilection. *Hepatology* 1999; 30(5):1144-50.

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

BEATRICE A KALLUNGAL  
03/29/2016

## Secondary Clinical Review

<b>Date</b>	2/17/2016
<b>From</b>	Donna Przepiorka, MD, PhD
	Office of Hematology and Oncology Products / Division of Hematology Products
<b>Application #</b>	<b>NDA 208114</b>
<b>Applicant</b>	Jazz Pharmaceuticals
<b>Date of Submission</b>	7/31/2015
<b>PDUFA Goal Date</b>	3/31/2015
<b>Proprietary Name</b>	Defitelio
<b>Established Name</b>	Defibrotide sodium
<b>Dosage form / Strength</b>	Injection (200 mg / 2.5 mL)
<b>Applicant Proposed Indication(s)/Population(s)</b>	For the treatment of patients with hepatic veno-occlusive disease (VOD), also known as sinusoidal obstruction syndrome (SOS), with <span style="background-color: #cccccc;">(b) (4)</span> dysfunction following hematopoietic stem-cell transplantation (HSCT).
<b>Recommendation on Regulatory Action</b>	Regular approval with a postmarketing requirement and a postmarketing commitment
<b>Recommended Indication(s)/Population(s)</b>	For the treatment of adult and pediatric patients with hepatic veno-occlusive disease (VOD), also known as sinusoidal obstruction syndrome (SOS), with renal or pulmonary dysfunction following hematopoietic stem-cell transplantation (HSCT).

<b>Additional Material Reviewed/Consulted</b>	<b>Primary Reviewer</b>
Medical Officer Review	Tanya Wroblewski, MD
Biostatistics	Cindy Gao, PhD

**Secondary Review (Clinical Team Leader)**

NDA 208114

Defitelio (defibrotide sodium)

**Table of Contents**

<b>Table of Contents .....</b>	<b>2</b>
<b>1. Recommended Regulatory Action.....</b>	<b>3</b>
<b>2. Product Information.....</b>	<b>3</b>
<b>3. Benefit-Risk Framework .....</b>	<b>3</b>
<b>4. Background .....</b>	<b>4</b>
<b>5. Clinical/Statistical - Efficacy .....</b>	<b>5</b>
<b>6. Clinical - Safety .....</b>	<b>10</b>
<b>7. Overall Benefit-Risk Assessment by the Secondary Reviewer .....</b>	<b>13</b>
<b>8. Recommendations for Labeling.....</b>	<b>14</b>
<b>9. Recommendations for Postmarket Requirements and Commitments .....</b>	<b>15</b>
<b>10. References .....</b>	<b>16</b>

**Table of Tables**

<b>Table 1. VOD Diagnostic Criteria .....</b>	<b>4</b>
<b>Table 2. Study 2005-01 Primary Endpoint – Primary and Sensitivity Analyses .....</b>	<b>7</b>
<b>Table 3. Outcomes for Patients with Hepatic VOD and MOF .....</b>	<b>9</b>

## Secondary Review (Clinical Team Leader)

NDA 208114

Defitelio (defibrotide sodium)

### 1. Recommended Regulatory Action

I concur with the recommendation of Dr. Tanya Wroblewski, the Primary Clinical Reviewer, of regular approval of defibrotide sodium under NDA 208114 (Defitelio) for the indication “For the treatment of adult and pediatric patients with hepatic veno-occlusive disease (VOD), also known as sinusoidal obstruction syndrome (SOS), with renal or pulmonary dysfunction<sup>1</sup> following hematopoietic stem-cell transplantation (HSCT).” The recommended dosing regimen for defibrotide sodium is 6.25 mg every 6 hours for a minimum of 21 days or until resolution of veno-occlusive disease for a maximum of 60 days.

### 2. Product Information

Defibrotide sodium (Defitelio) is a polydisperse mixture of predominately single-stranded polydeoxyribonucleotide sodium salts derived from porcine intestinal tissue. Defibrotide sodium demonstrated profibrinolytic properties in vitro and altered the response of cultured endothelial cells to chemotherapy-induced effects, but the exact mechanism of action is not fully understood.

### 3. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<ul style="list-style-type: none"><li>• VOD with MOF occurs in &lt;2% of patients after HSCT.</li><li>• For patients who develop VOD with MOF, survival at Day 100 after HSCT was reported as 21-31%.</li></ul>	VOD with MOF is a rare disorder, and it has a very high early mortality rate.
Current Treatment Options	<ul style="list-style-type: none"><li>• There are currently no drugs approved for treatment of VOD with MOF.</li></ul>	There is a substantial need for an effective therapy for VOD with MOF.
Benefit	<ul style="list-style-type: none"><li>• In 2 prospective trials and 1 expanded access protocol, defibrotide sodium 6.25 mg/kg iv every 6 hr was given to patients having VOD with MOF after HSCT.</li><li>• The 3 studies accrued 102, 75 and 351 subjects, respectively.</li><li>• Survivals at Day 100 after HSCT were 38%, 44% and 45%.</li></ul>	Although there is uncertainty when interpreting survival in a single-arm trial, the 3 studies showed survival rates consistently higher than reported previously for this population.
Risks	<ul style="list-style-type: none"><li>• Hemorrhage and hypersensitivity are known potential serious adverse reactions of defibrotide sodium.</li><li>• In the 176 subjects in the selected safety population, no other suspected adverse reactions were identified.</li><li>• VOD with MOF has high background rate of adverse events</li><li>• Investigators were not asked to report all adverse events.</li></ul>	The lack of comparative safety data from a randomized trial, and the lack of immunogenicity studies leave uncertainty about the safety profile of defibrotide, but the apparent survival benefit outweighs the potential risks
Risk Management	<ul style="list-style-type: none"><li>• The risk of serious adverse reactions was minimized in the clinical studies by mandated monitoring for such risks, dose interruptions if a potential adverse reaction occurred, and prohibition of concurrent use of antithrombotic agents.</li></ul>	Labeling should include warnings for hemorrhage and hypersensitivity, and a contraindication of concurrent use with antithrombotic agents.

<sup>1</sup> Within this review, hepatic veno-occlusive disease with renal or pulmonary dysfunction will be referred to as VOD with MOF.

## Secondary Review (Clinical Team Leader)

NDA 208114

Defitelio (defibrotide sodium)

### 4. Background

Hepatic VOD is a clinical syndrome marked by hepatomegaly, right upper quadrant pain, weight gain, ascites and elevated bilirubin occurring shortly after exposure to an agent toxic to the liver. The earliest histological changes include rounding up of the sinusoidal endothelial cells in zone 3 of the hepatic acinus, allowing extravasation of fluid and cell debris into the subendothelial space of Disse leading to obstruction of flow from the portal vein to the central vein in the hepatic lobule (DeLeve, Shulman, et al. 2002). The process may extend into and occlude the central vein and/or contribute to necrosis of the perivenular hepatocytes. A later phase is marked by subendothelial collagenization, which if extensive results in fibrous bridging. In a correlative pathology study, the clinical severity of hepatic VOD was associated with hepatocyte necrosis, sinusoidal fibrosis and luminal sclerosis (Shulman, Fisher, et al. 1994). The pace of healing after such an injury is not well-characterized.

The high-dose chemotherapy or chemoradiotherapy used for allogeneic or autologous HSCT is cited as one of the most common causes of hepatic VOD. Two sets of criteria, the Seattle criteria and the Baltimore criteria (Table 1, from Dr. Wroblewski's review), are in wide use for diagnosis of hepatic VOD in the HSCT setting, and both require exclusion of other potential etiologies of the signs and symptoms listed.

**Table 1. VOD Diagnostic Criteria**

Seattle Criteria (McDonald, 1984 Hepatology)	Baltimore Criteria (Jones, 1987 Transplantation)
Presence before day 20 after hematopoietic stem cell transplantation(HSCT) of 2 or more of the following: <ul style="list-style-type: none"><li>• Bilirubin<math>\geq</math>2mg/dl</li><li>• Hepatomegaly, right upper the quadrant(RUQ) pain</li><li>• Ascites +/- unexplained weight gain of <math>&gt;</math> 2% baseline</li></ul>	Hyperbilirubinemia $\geq$ 2mg/dl before day 21 after HSCT and at least 2 of the following: <ul style="list-style-type: none"><li>• Hepatomegaly(usually painful)</li><li>• Ascites</li><li>• Weight gain <math>\geq</math> 5% from baseline</li></ul>

Source: Dr. Wroblewski's review

In a side-by-side application of both sets of diagnostic criteria for a cohort of patients undergoing allogeneic HSCT, the Seattle criteria identified a slightly higher proportion of patients as having hepatic VOD (14% vs 9%), but the number of patients having VOD with MOF was the same using either set of criteria (3%) (Carreras, Diaz-Beya, et al. 2011). Plasminogen activator inhibitor-1 (PAI-1) has been suggested as a diagnostic marker for hepatic VOD, but although it has a good negative predictive value, the specificity is poor (Pihusch, Wegner, et al. 2005). Panels of other diagnostic and prognostic biomarkers for hepatic VOD have been identified by proteomics, but these have not yet been validated (Akil, Zhang, et al. 2015).

Various criteria have been used to classify the clinical severity of hepatic VOD after HSCT, but the definition of severe VOD used most commonly was a demonstration of adverse effects from

## Secondary Review (Clinical Team Leader)

NDA 208114

Defitelio (defibrotide sodium)

liver disease with persistent signs and symptoms that do not resolve by Day 100 after HSCT or with death before Day 100 after HSCT (Coppell, Richardson, et al. 2010). This definition suffers from the requirement that it be applied retrospectively after the course through Day 100 is known. There is, however, a consistent correlation between the occurrence of MOF and the severe class of hepatic VOD (McDonald, Hinds, et al. 1993; Coppell, Richardson, et al. 2010), suggesting that MOF would be a valuable classification criterion that could be applied in real time.

The incidence of hepatic VOD is highly variable across publications, likely due to differences in risk factors in the patient populations under study as well as differences in diagnostic criteria between publications (Coppell, Richardson, et al. 2010; Dalle, Giralt 2016). Overall, however, severe hepatic VOD is a rare complication after HSCT. The applicant submitted a report from the CIBMTR which indicated for 19,346 patients transplanted in the US 2008-2014 for which they have records, the incidence of hepatic VOD was 3.4%, and 320 patients (1.7%) were reported as having severe hepatic VOD (Response to Information Request received 11/20/2015).

The prognosis of patients with severe hepatic VOD after HSCT is poor. The reported survival of these patients is less than 20% (Coppell, Richardson, et al. 2010). There is currently no available therapy in the US for treatment of severe hepatic VOD, and the use of any approved drugs as standard of care for this disorder has not been established in any of the randomized trials that have been conducted.

### 5. Clinical/Statistical - Efficacy

The statistical reviewer (Dr. Cindy Gao) could not confirm the applicant-reported treatment effect of defibrotide in the treated cohort vs. the historical control cohort in Study 2005-01 for inference purpose, but she did confirm that there was a numerically higher Day-100 survival rate in favor of the defibrotide-treated cohort and concluded that whether or not the results represent a favorable benefit to risk to support an approval of defibrotide is deferred to clinical judgment.

The clinical reviewer (Dr. Tanya Wroblewski) concluded that the totality and consistency of survival at Day 100 after HSCT in Studies 2005-01, 99-118, 2006-05 and CIBMTR provided substantial evidence to support approval of this application.

This section of the Secondary Clinical Review is derived in part from Dr. Gao's review and Dr. Wroblewski's review. The major issue addressed in this section is characterization of the available evidence of effectiveness of defibrotide sodium for treatment of hepatic VOD (b) (4) after HSCT. The comprehensive details of the results of the clinical studies reported by Dr. Wroblewski and Dr. Gao will not be repeated here.

The pivotal study in support of this NDA was Study 2005-01 "Defibrotide for the Treatment of Severe Hepatic Venous Occlusive Disease in Hematopoietic Stem Cell Transplant Patients: A Historically-Controlled, Multi-Center Phase 3 Study to Determine Safety and Efficacy." Eligible subjects included those who met the Baltimore diagnostic criteria for VOD by Day + 21 post-

## Secondary Review (Clinical Team Leader)

NDA 208114

Defitelio (defibrotide sodium)

HSCT and who fulfilled the criteria for pulmonary and/or renal dysfunction. Treatment consisted of defibrotide sodium 6.25 mg/kg every 6 hours for a minimum of 21 days and until the patient was discharged from the hospital.

Subjects in the defibrotide group were followed through discharge from the hospital and then on Day 100 and Day 180 after HSCT for survival and response assessments. Response was assessed clinically on the basis of ascites, hepatomegaly, right upper quadrant pain, and bilirubin. Subjects in the historical control group were selected by chart review of all consecutive patients transplanted at the participating centers but who did not enroll in the defibrotide group. The inclusion and exclusion criteria were prespecified in the protocol and similar for both groups. For patients who met the screening criteria as potential historical control subjects, narratives, inclusion case report forms and partially redacted medical records were reviewed by a blinded Medical Review Committee (MRC) to ensure that inclusion and exclusion criteria were met. There was no assessment schedule for the historical controls; available data was to be abstracted retrospectively from the medical charts and recorded on the case report forms.

The primary objective of Study 2005-01 was to demonstrate the efficacy of defibrotide sodium in patients with severe VOD in terms of survival at Day 100 after HSCT in patients who received defibrotide sodium (defibrotide group) compared to an historical control group not treated with defibrotide sodium. The key secondary objective was to compare the complete response (CR) rate by Day 100 post-HSCT in the defibrotide group versus the historical control group. The original planned sample size was 80 subjects in each group. The planned primary analysis was a propensity-stratified Koch weighted 95.1% confidence interval of the treatment difference in the binary incidences of the endpoints in the ITT population. The covariates to be used in the propensity score included a) ventilator and/or dialysis dependent, b)  $\leq$  or  $>$  16 years of age, c) allogeneic or autologous transplantation, and d) prior stem cell transplantation.

There were multiple revisions to the protocol and the statistical analysis plan, including changes in the primary endpoint, after completion of the study and analysis of the data. Due to these revisions and changes in the study schedule, raw data for assessment of CR was not available for all study subjects. Therefore, CR will not be considered further in this review. As described above, survival at Day 100 after HSCT was the primary endpoint, and the final revision to the protocol was agreed upon with the FDA.

There were 102 subjects accrued to the defibrotide group with enrollment from 7/26/2006 and follow-up through 11/19/2008. For the historical controls, 6867 charts were screened, and 123 patients were identified as potential controls. After 2 review cycles by the MRC, there were 32 confirmed patients in the historical control group (transplanted 1995-2007).

Survival at Day 100 after HSCT was 38% in the defibrotide group and 25% for the historical controls. The estimated difference in survival calculated by the applicant using the propensity-stratified Koch weighted estimate was (b) (4) % with a (b) (4) % confidence interval of (b) (4) % to (b) (4) % (b) (4) which they concluded demonstrated a significant treatment effect for defibrotide sodium.

## Secondary Review (Clinical Team Leader)

NDA 208114

Defitelio (defibrotide sodium)

Dr. Gao identified a number of statistical issues in the analysis of Study 2005-01:

- Whether or not the propensity score adjusted analysis have sufficiently balanced the between treatment difference cannot be determined.
- Koch's method does not allow for a sample size of 1 or smaller in any of the propensity score stratum and a size of 1 is observed in one of the stratum in the sponsor's primary analysis, therefore the [statistical]reviewer does not consider the sponsor's primary analysis adequate.
- The property of the propensity score adjusted analysis method is not known when sample size is small and distribution of the strata level is sparse. Therefore, the applicant's interpretation of the primary efficacy results is questionable.
- Sensitivity analyses of day + 100 survival rate varied by which propensity score strata were used. The nominal p-values from the sensitivity analyses ranged from (b) (4) to (b) (4) so the sensitivity analyses could not confirm the sponsor's primary analysis results.

**Table 2. Study 2005-01 Primary Endpoint – Primary and Sensitivity Analyses**

Propensity Score Group	Difference in Survival (Treatment-Control) at Day-100 after HSCT	Nominal P-Value*
<b><u>Sponsor's Primary Analysis</u></b>		
Quintile	23.0% (5.2%, 40.8%)	(b) (4)
<b><u>Sponsor's Sensitivity Analyses</u></b>		
Quintile, and adjusted for 4 prognostic factors and additional other factors	10.6% (-13.6%, 34.8%)	(b) (4)
Quartile	18.3% (-0.2%, 36.3%)	(b) (4)
Quartile and adjusted for 4 prognostic factors and additional other factors	14.7% (-7.8%, 37.2%)	(b) (4)
<b><u>Reviewer's Sensitivity Analyses</u></b>		
Quartile/Quintile Group ('high')	20.1% (2.1%, 38.2%)	(b) (4)
Quartile/Quintile Group ('low')	21.1% (3.4%, 38.8%)	(b) (4)
Equal space quintile	17.6% (-1.1%, 36.3%)	(b) (4)
Equal space quartile	16.1% (-1.6%, 33.8%)	(b) (4)
Unadjusted	13.2% (-4.6%, 31.0%)	(b) (4)

Source: Dr. Gao's review

\*Not corrected for multiple interim analyses

- The significance level cannot be determined due to many unplanned adaptations, e.g. sample size reduction and planned/unplanned interim analyses.

I agree with Dr. Gao's conclusions that the sample size of the control group is too small and does not fulfill the protocol's original design requirements, the statistical methodology applied is

## Secondary Review (Clinical Team Leader)

NDA 208114

Defitelio (defibrotide sodium)

questionable in view of the irregular sample distribution by stratum, the results of the analysis of the primary endpoint are not robust (Table 2), and the type 1 error has not been controlled for the multiple planned and unplanned interim analyses. The results of Study 2005-01 as conducted and analyzed would therefore not be considered evidence of effectiveness of defibrotide sodium for treatment of hepatic VOD (b) (4) after HSCT sufficient to support approval of an NDA.

Dr. Wroblewski concluded in her Integrated Assessment of Effectiveness that the totality of survival data from study 2005-01 supported by the survival data from Study 99-118, expanded access IND study (2006-05), and registry data from CIBMTR support the recommendation of regular approval of the marketing application for defibrotide sodium.

The additional studies submitted by the applicant included the following:

- Study 99-118 was an open-label, randomized, dose-finding study of defibrotide sodium. VOD was diagnosed using the Baltimore criteria, and severity was determined on the basis of Bearman risk of severe VOD at least 30%, or the presence of renal, pulmonary or central nervous system dysfunction. Treatment was administered for at least 14 days. There were 75 subjects enrolled on the 25 mg/kg/day arm of the trial between 4/2000 and 5/2007, and 44% of patients in this arm survived through Day 100 after HSCT.
- Study 2006-05 is an expanded access protocol for treatment of patients with VOD diagnosed by the Baltimore criteria, the Seattle criteria, or biopsy. The patients were treated with defibrotide sodium 25 mg/kg/day for at least 21 days. Survival at Day 100 after HSCT was a prespecified outcome parameter for the subset of patients treated for VOD after HSCT. Between 12/14/2007 and 12/31/2013, there were 649 patients treated, of whom 351 had VOD with renal or pulmonary dysfunction after HSCT. For the latter subgroup, survival at Day 100 after HSCT was 45%.
- Study CIBMTR was an analysis of registry data extracted from the CIBMTR Research Database. The diagnosis of VOD was as reported on Form 2100, and MOF was determined by the occurrence of renal or pulmonary organ impairment as reported on Form 2100. There were 8,341 transplantations reported 11/1/2008 – 12/31/2011. Of these, 96 were identified as having VOD with MOF, including 41 treated with defibrotide sodium (dose and duration not stated) and 55 who did not receive defibrotide sodium. There was a numerically higher survival at Day 100 after HSCT in the defibrotide cohort (39% vs 31%), but since the dose and schedule of defibrotide sodium were not specified, the applicability of the survival outcome is unclear.
- Study DF-CUP was an analysis of data from the applicant's compassionate use program. There were 710 patients known to have been treated with defibrotide sodium under this program from 1/2006 to 7/2009. For these treatments, defibrotide sodium was started at 10 mg/kg/day and escalated to 25, 40, 60 or 80 mg/kg/day at the discretion of the treating physician. Although the physicians were required to report outcomes to the local regulatory agencies as required by local law, reporting to the applicant was voluntary. Data integrity could not be confirmed, so this study was not considered further in the evaluation of effectiveness of defibrotide sodium.

## Secondary Review (Clinical Team Leader)

NDA 208114

Defitelio (defibrotide sodium)

- Study 2004-000592-33 (Study 2004) was an open-label, randomized, Phase 3 study of defibrotide vs no treatment for prevention of VOD in patients at high risk of developing VOD after HSCT. In the treatment group, defibrotide sodium was given at 25 mg/kg/day from the start of conditioning to Day 30 after HSCT. There were 356 subjects randomized (180 to defibrotide prophylaxis and 176 to the control arm). The subjects on the defibrotide arm had a numerically lower incidence of VOD by Day 30 after HSCT (12% vs 20%). Although the results of this study may suggest that defibrotide sodium is an active drug, the activity tested is not applicable to the indication under review in the present NDA, so it will not be considered further.

Table 3 shows the outcomes for the subjects treated with defibrotide sodium 25 mg/kg/day on Studies 2005-01, 99-118 and 2006-05. The survivals at Day 100 after HSCT ranged from 38% to 45% in these studies. The study populations vary with regard to factors considered important for the survival outcome, but the results in all of the studies were higher than expected for patients with hepatic VOD and MOF after HSCT.

**Table 3. Outcomes for Patients with Hepatic VOD and MOF**

	<u>Treated with Defibrotide Sodium 25 mg/kg/day</u>			<u>No Treatment with Defibrotide Sodium</u>		
	<b>Study 2005-01 (n=102)</b>	<b>Study 99-118 (n=75)</b>	<b>Study 2006-05 (n=351)</b>	<b>Study 2005-01 (n=32)</b>	<b>Study CIBMTR (n=55)</b>	<b>Coppell<sup>b</sup> (n=38)</b>
<b><u>Study Type</u></b>	Prospective	Prospective	Expanded Access	Retrospective	Registry Analysis	Survey
<b><u>Subjects</u></b>						
Median Age (Range)	21 yrs (<1 – 72 yrs)	32 yrs (<1 – 61 yrs)	15 yrs (1-69 yrs)	18 yrs (1-57 yrs)	31 yrs (<1-67 yrs)	-
Age <17 yrs	43%	29%	54%	44%	25%	-
Allo HSCT	88%	89%	90%	84%	96%	-
Vent/Dial <sup>a</sup>	33%	11%	42%	22%	87%	-
<b><u>Outcome</u></b>						
Survival at Day 100 (95% CI)	38% (29% - 48%)	44% (33% - 55%)	45% (40% - 51%)	25% (12% - 43%)	31% (19% - 45%)	21% (10% - 37%)

Source: Secondary reviewer analysis

<sup>a</sup>Ventilator- or dialysis-dependent

<sup>b</sup>Coppell, Richardson, et al. 2010

Table 3 also shows the outcomes for 3 groups of patients with hepatic VOD and MOF after HSCT who were not treated with defibrotide sodium. The use of historical controls might be acceptable for study of a new treatment in a rare population where the historical outcomes are well-characterized and consistent over time, especially if there is a large treatment effect for the new therapy. However, even in such a circumstance, an optimal source of controls would be from a prior prospective trial with selection and monitoring of the subjects using the same procedures as in the current trial. Unfortunately, there is no such study of treatment of patients

## **Secondary Review (Clinical Team Leader)**

NDA 208114

Defitelio (defibrotide sodium)

with hepatic VOD and MOF in the current era, so alternative sources would be needed to confirm that the published survival rates without defibrotide treatment are still accurate.

There are potential pitfalls in the selection of patients not treated with defibrotide sodium in Table 3. As discussed above, the historical controls for Study 2005-01 were finalized after analyses of survival using a larger group of patients which had a better survival rate, raising a concern that there may have been bias in the selection of the final cohort. However, as indicated by Dr. Wroblewski in her review: “A review of the narratives by this reviewer for the 54 patients excluded from the final MRC review concluded that an alternate etiology for symptomology could be explained. Thus, the enrollment of these 54 patients into the final control group would not have represented the appropriate population for this trial.” The selections of the controls from the CIBMTR analysis and the survey by Coppell, et al. were based on the reports from the transplant center, and the data were not confirmed by inspection of the source documents, but the consistency of the results in the 3 groups of patients supports the verity of the survival rates displayed. Nonetheless, in the absence of randomization or other methods to minimize bias, direct comparisons between the subjects in the defibrotide sodium studies with the external cohorts not treated with defibrotide sodium would not be acceptable for more than exploratory purposes.

It was disappointing that the raw data needed for the response assessment to corroborate the activity of this drug was not available. Overall, however, the data demonstrated that for patients with hepatic VOD and MOF treated with defibrotide sodium 25 mg/kg/day, the survivals at Day 100 after HSCT were numerically higher than expected from published data and independent sources of patient-level data. A point-in-time survival rate in a single-arm trial is not generally used as the basis for a regular approval, but given that a) hepatic VOD with MOF is an early event after HSCT, b) it is well-established that there is a high early mortality with this disorder, and c) there are many other complications of HSCT not treated by defibrotide sodium that affect later mortality, Dr. Wroblewski’s determination that Day-100 survival adequately reflects a durable effect of the drug is likely valid. I therefore agree with Dr. Wroblewski’s conclusion that the totality of the evidence supports the effectiveness of defibrotide sodium for treatment of the intended population.

## **6. Clinical - Safety**

I personally evaluated the safety data submitted to this NDA. This section of the Secondary Clinical Review is derived in part from the Integrated Assessment of Safety in the Primary Clinical Review.

The safety information was reviewed for 1894 individuals exposed to defibrotide sodium in seven sponsored studies or trials of treatment of VOD, treatment of other disorders, prevention of VOD, or evaluations of PK and PD. One QT study was conducted in healthy volunteers. This safety information was supplemented by a retrospective registry study, available published literature, legacy clinical study reports, and postmarketing information for all formulations of defibrotide.

## Secondary Review (Clinical Team Leader)

NDA 208114

Defitelio (defibrotide sodium)

The types of safety data recorded (deaths, serious adverse events, adverse events of interest, common adverse events, adverse event characterization, common laboratory tests and vital signs) varied by protocol. None of the trials in patients with VOD collected all treatment-emergent adverse events. The best available adverse event information to assess safety of the proposed dose in the intended population was pooled data from 176 subjects with hepatic VOD and MOF after HSCT treated with defibrotide sodium 6.25 mg/kg intravenously every 6 hours (total 25 mg/kg/day) in Studies 2005-01 and 99-118. This group is called the Selected Safety Population (SSP).

There were 105 males and 71 females with hepatic VOD and MOF after HSCT in the SSP. The median age was 25 years (range, 0.1-72 years). Pediatric patients comprised 37%, and there was a single subject > 65 years old. Twenty-four percent of the subjects were ventilator- or dialysis-dependent. The subjects were treated with defibrotide sodium for a median of 21 days (range, 1-83 days). In general, the safety analyses for the SSP revealed no events unexpected for patients with hepatic VOD and MOF after HSCT. However, a high rate of emerging adverse events, including grade 4-5 adverse events, is expected in this population independent of the intervention, and this may prohibit identification of adverse reactions with small to moderate increases in risk.

Hemorrhage is a clear potential serious adverse reaction for defibrotide sodium based on its pharmacologic effects and the apparent dose-toxicity relationship. In the SSP, events in the SMQN Hemorrhages (excluding laboratory terms) occurred in 59% of subjects, and the events were grade 4-5 for 20%. The most common Preferred Terms for hemorrhage were epistaxis (14%), gastrointestinal hemorrhage (9%), hematuria (9%), and pulmonary alveolar hemorrhage (9%). The applicant noted that these event rates were comparable to those reported in the literature, and that by their analysis, hemorrhage events were less frequent on the defibrotide arm than on the control arm in Study 2005-01, suggesting that the proposed dose of 6.25 mg/kg every 6 hours is tolerable in this population. To ensure that safe use can be recapitulated in practice, the Prescribing Information should contain at least the same levels of controls as the protocols with regard to warnings, patient selection, monitoring, and treatment interruption for bleeding or invasive procedures.

Hypersensitivity is a second potential serious adverse reaction for defibrotide sodium. There were no immunogenicity studies performed. On analysis of clinical outcomes, events in the SMQN Hypersensitivity that were listed as related occurred in 1% of subjects in the SSP and <1% in Other Defibrotide-Treated Patients in the safety population. The majority of these events were types of rash, but further characterization was not possible due to the lack of narrative for these events. In three large (>1000 subjects treated with defibrotide) trials testing the efficacy of defibrotide (pre-1995 product) 200 mg intravenously 4 times a day or 400 mg intravenously twice daily for thromboembolic prophylaxis through 7 days after surgical procedures, the incidences of allergic reactions in the defibrotide-treated subjects were 0.5% to 0.8%. There was also one published case report of anaphylaxis after intravenous infusion of 200 mg of defibrotide, and hypersensitivity in this case was confirmed later by skin test. Although the

## Secondary Review (Clinical Team Leader)

NDA 208114

Defitelio (defibrotide sodium)

incidence of hypersensitivity reactions is low, the occurrence of anaphylaxis warrants a warning in the Prescribing Information.

Hypotension was also proposed by the applicant as a potential adverse reaction of defibrotide sodium. Although hypotension was the most frequent treatment-emergent adverse event reported in the SSP, it is also common in this population independent of treatment, and there were no data suggesting that the rate of hypotension was greater with defibrotide sodium. It should be noted, however, that the vital sign monitoring schedule was not appropriate to allow detection of infusion-related reactions such as hypotension, so the absence of this risk will need to be confirmed with an appropriate study.

The applicant also provided comparative analyses of safety data vs the historical controls in Study 2005-01 and in the randomized prophylaxis study, Study 2004. Overall, there were no substantial and consistent adverse effects of defibrotide sodium when used as treatment or prevention of VOD in the HSCT recipients in comparison to safety outcomes in the respective control groups as assessed by the applicant. In support of a conclusion that defibrotide sodium is safe, in two large (>1000 subjects) trials testing the efficacy of defibrotide 200 mg (pre-1995 material) intravenously 4 times a day for thromboembolic prophylaxis after surgical procedures, the incidences of adverse reactions reported were low (<1% and 1.3%). The lack of completeness of the safety data in Studies 2005-01 and 2004 diminishes the reliability of the negative results for these comparative analyses, and the credibility of the comparisons for Study 2005-01 is further weakened by the disparities in the procedures for collection of safety data for the treatment and control cohorts. The published results from the large thromboembolic prophylaxis studies provide only minimal support for the safety of defibrotide sodium, since the lack of adverse reactions in those studies may simply reflect the much lower and potentially less toxic dose (~11 mg/kg/day) used in comparison to that in the VOD treatment trials (25 mg/kg/day).

In the assessment of safety in special populations, there was an inverse trend for pulmonary hemorrhage with age for the subjects in the VOD treatment trials, but this trend was not confirmed in the prophylaxis phase of the VOD prevention trial. There was not a sufficient number of geriatric subjects in the safety database to allow for a meaningful analysis in this subgroup. There was a higher incidence of hemorrhage events and hypotension during defibrotide sodium treatment in patients who were dialysis- or ventilator-dependent, but this could not be ascribed to defibrotide sodium specifically, since the same trend was seen in the control group in Study 2005-01.

No formal drug-drug interaction studies were conducted by the applicant. Reports from the published literature showed that defibrotide enhanced the activity of dabigatran, unfractionated heparin or low molecular weight heparin *ex vivo* in human blood or plasma and in one clinical study in healthy volunteers. The pharmacologic activity of defibrotide suggests that it might also be expected to enhance the activity of fibrinolytic agents. The increased risk of bleeding due to these effects of defibrotide contra-indicates concurrent use with anticoagulants and fibrinolytic therapies. In a murine model of induced thromboembolism, tranexamic acid counteracted the

## **Secondary Review (Clinical Team Leader)**

NDA 208114

Defitelio (defibrotide sodium)

protective effect of defibrotide. Although this interaction is biologically plausible, there are no confirmatory clinical data.

There were no additional unexpected serious adverse events reported in the postmarket setting since the approval of defibrotide sodium in Europe in 2013 for treatment of severe hepatic VOD following HSCT. The majority of the related serious adverse events reported involved bleeding or coagulopathy. There were similarly few related unexpected serious adverse events recorded in the periodic safety updates for the years 1995-2008 for the other formulations of defibrotide marketed in Italy.

In summary, there was a high rate of adverse reactions in the patients being treated for hepatic VOD with MOF using the proposed dose-schedule of defibrotide sodium, but there was no consistent signal that any of the events was caused specifically by defibrotide sodium. The published reports of safety of defibrotide in other populations and the review of the postmarket reports are consistent with the relative tolerability of defibrotide sodium in the VOD trials. Hemorrhage, hypersensitivity and pharmacologic interaction with anticoagulants and fibrinolytic therapies are serious safety concerns, but these can be mitigated by appropriate warnings, contraindications and instructions for patient selection and dose modifications in the Prescribing Information. The lack of complete safety data from a well-conducted randomized trial is a substantial deficiency that raises questions about the accuracy of the safety profile in the intended population as currently established, and this residual concern needs to be considered when weighing the overall risks and clinical benefits of this therapy.

### **7. Overall Benefit-Risk Assessment by the Secondary Reviewer**

Hepatic VOD with MOF after HSCT is a rare disorder with a very high early mortality. The applicant has provided results from 3 single-arm studies in which patients with hepatic VOD and MOF were treated with defibrotide sodium, and the survivals at Day 100 after HSCT were 38% to 45%, which is higher than expected for this population. While none of these studies alone would be considered an adequate demonstration of the effectiveness of defibrotide sodium, taken together they form a reasonable basis for approval.

Hemorrhage, hypersensitivity and pharmacologic interaction with anticoagulants and fibrinolytic therapies are established serious safety concerns for defibrotide sodium. In the clinical trials, these risks were moderated in part by exclusion of patients at high risk, close monitoring and dose interruption for bleeding, other adverse reactions or invasive procedures, and prohibition of concurrent use with antithrombotic agents. These strategies would be needed for safe use of the drug in practice, and this can likely be accomplished with explicit instructions in labeling.

The lack of complete safety data from a well-conducted randomized trial and the lack of immunogenicity studies are substantial deficiencies that are allayed in part by the history of safe use of defibrotide sodium in the postmarketing period after approval in Europe and for the other formulations of defibrotide previously approved in Italy. Nonetheless, having an accurate safety profile would be of value for decision-making discussions between patients with this serious

**Secondary Review (Clinical Team Leader)**

NDA 208114

Defitelio (defibrotide sodium)

disorder and their healthcare providers. However, based on the available safety and effectiveness data, the lack of alternative treatments, and the poor prognosis of this patient population, the potential toxicities and residual uncertainties are outweighed by the potential benefit of treatment with defibrotide sodium for patients with hepatic VOD (b) (4) after HSCT.

**8. Recommendations for Labeling**

Dr. Wroblewski made the following recommendations for major changes in labeling:

• **INDICATIONS AND USAGE**

- Added “pediatric”: Defitelio is indicated for the treatment of adult and pediatric patients with hepatic veno-occlusive disease also known as sinusoidal obstruction syndrome (SOS) with (b) (4) renal (b) (4) pulmonary dysfunction following hematopoietic stem cell transplantation

• **DOSAGE AND ADMINISTRATION**

- The recommended dosing regimen for defibrotide is 6.25 mg every 6 hours for a minimum of 21 days or until resolution of veno-occlusive disease.

(b) (4)

• **WARNINGS AND PRECAUTIONS**

(b) (4)

• **USE IN SPECIFIC POPULATION**

- Changes consistent with the Pregnancy and Lactation Labeling Rule

(b) (4)

**Recommendation of the Secondary Reviewer:** In general, I agree with Dr. Wroblewski’s recommendations for the sections identified above, with the following exceptions:

- Indicate in Section 2 that treatment is limited to no more than 60 days, since safety and efficacy data to support a longer duration of treatment are not available.
- Add to Section 2 an assessment of the patient to exclude those with active bleeding or hypotension.
- Include in Section 5 Warnings and Precautions for hemorrhage and hypersensitivity, which are clear risks of treatment with defibrotide sodium.
- Do not display (b) (4) (b) (4) (b) (4)
- Display all adverse events, (b) (4), from the SSP as adverse reactions in Section 6, since the available single-arm data do not allow for exclusion of any other events as not related.

**Secondary Review (Clinical Team Leader)**

NDA 208114

Defitelio (defibrotide sodium)

For Section 14, Dr. Wroblewski made the following recommendations:

[Redacted] (b) (4)

- [Redacted] (b) (4)
- Only descriptive statistics will be used for primary endpoint.

For Section 14, Dr. Gao made the following recommendations:

- ...excluding [Redacted] (b) (4) in the label
- ...reporting the exact confidence interval of day + 100 survival rate, [Redacted] (b) (4)

[Redacted] (b) (4)

**Recommendation of the Secondary Reviewer:** As discussed in Section 6 above, I agree with the concerns expressed by Dr. Gao regarding the interpretability of the comparison of survival at Day 100 after HSCT in Study 2005-01. In fact, as stated in Section 7 above, since the evidence that supports the approval of defibrotide sodium is not a direct comparison between cohorts in 2005-01 but rather the consistent survival rates across studies in comparison to reported outcomes, I would recommend displaying in labeling the descriptive survival outcomes from the 3 defibrotide studies that utilized the recommended 25 mg/kg/day dose (2005-01, 99-118 and 2006-05) [Redacted] (b) (4)

**9. Recommendations for Postmarket Requirements and Commitments**

Dr. Wroblewski made the following recommendations for postmarket requirements and commitments:

PMR #1 Description: Conduct an analysis of safety in a randomized, open-label multi-center clinical trial comparing defibrotide versus best supportive care in the prevention of hepatic VOD in adult and pediatric patients, including all adverse events, laboratory abnormalities and frequent peri-infusion vital signs.

PMC #1 Description: Develop sensitive and specific anti-drug (defibrotide) binding and neutralizing assays. Submit Validation reports on the assays in a final report to the NDA.

## Secondary Review (Clinical Team Leader)

NDA 208114

Defitelio (defibrotide sodium)

PMC #2 Description: Evaluate patient's sera for binding and neutralizing antibodies to defibrotide using the validated assays from PMC 1 and submit the data in a final immunogenicity study report.

**Recommendation of the Secondary Reviewer:** I agree that postmarket requirements and commitments as recommended by Dr. Wroblewski will address the current uncertainties in the safety profile of defibrotide sodium.

## 10. References

Akil A, Zhang Q, Mumaw CL, et al. (2015) Biomarkers for diagnosis and prognosis of sinusoidal obstruction syndrome after hematopoietic cell transplantation. *Biol Blood Marrow Transplant* 21:1739-1745.

Carreras E, Diaz-Beya M, Rosinol L, et al. (2011) The incidence of veno-occlusive disease following allogeneic hematopoietic stem cell transplantation has diminished and the outcome improved over the last decade. *Biol Blood Marrow Transplant* 17: 1698-1720.

Coppell JA, Richardson PG, Soiffer R, et al. (2010) Hepatic veno-occlusive disease following stem cell transplantation: Incidence clinical course, and outcome. *Biol Blood Marrow Transplant* 16: 157-168.

Dalle J-H, Giralt SA. (2016) Hepatic veno-occlusive disease after hematopoietic stem cell transplantation: Risk factors and stratification, prophylaxis and treatment. *Biol Blood Marrow Transplant* 22: 400-409.

DeLeve L, Shulman H, McDonald G. (2002) Toxic injury to hepatic sinusoids: Sinusoidal obstruction syndrome (veno-occlusive disease). *Sem Liver Dis* 1: 27-41.

McDonald GB, Hinds MS, Fisher LD, et al. (1993) Veno-occlusive disease of the liver and multi-organ failure after bone marrow transplantations: a cohort study of 355 patients. *Ann Intern Med* 118:255-267.

Pihusch M, Wegner H, Goehring P, et al. (2005) Diagnosis of hepatic veno-occlusive disease by plasminogen activator inhibitor-1 plasma antigen levels: A prospective analysis in 350 allogeneic hematopoietic stem cell recipients. *Transplant* 80:1376-1382.

Shulman HM, Fisher LD, Schoch HG, et al. (1994) Veno-occlusive disease of the liver after marrow transplantation: Histological correlates of clinical signs and symptoms. *Hepatology* 19: 1171-1181.

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

DONNA PRZEPIORKA  
02/17/2016

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

### CLINICAL REVIEW

<b>Application Type</b>	New Drug Application
<b>Application Number(s)</b>	208114
<b>Priority or Standard</b>	Priority
<b>Submit Date(s)</b>	31 July 2015
<b>Received Date(s)</b>	31 July 2015
<b>PDUFA Goal Date</b>	31 March 2016
<b>Division/Office</b>	Division of Hematology Products/OHOP
<b>Reviewer Name(s)</b>	Tanya Wroblewski, M.D. and Donna Przepiorka, M.D., Ph.D.
<b>Review Completion Date</b>	11 February 2016
<b>Established Name</b>	Defibrotide sodium
<b>(Proposed) Trade Name</b>	Defitelio
<b>Applicant</b>	Jazz Pharmaceuticals
<b>Formulation(s)</b>	Injection (200 mg / 2.5 mL)
<b>Dosing Regimen</b>	6.25 mg/kg intravenously every 6 hours via a 2 hour infusion, to be administered for a minimum of 21 days.
<b>Applicant Proposed Indication(s)/Population(s)</b>	Treatment of hepatic veno-occlusive disease (VOD), also known as sinusoidal obstruction syndrome (SOS), with <span style="background-color: gray; color: gray;">(b) (4)</span> dysfunction following hematopoietic stem-cell transplantation (HSCT).
<b>Recommendation on Regulatory Action</b>	Regular Approval
<b>Recommended Indication(s)/Population(s)</b>	Treatment of adult and pediatric patients with hepatic veno-occlusive disease (VOD), also known as sinusoidal obstruction syndrome (SOS), with renal or pulmonary dysfunction following hematopoietic stem cell transplantation (HSCT).

**Note:** Throughout this review, the term defibrotide refers to defibrotide sodium. The doses of defibrotide indicated in the description of clinical study designs or results are provided as stated in the studies.

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

## Table of Contents

Glossary.....	11
1 Executive Summary .....	14
1.1. Product Introduction.....	14
1.2. Conclusions on the Substantial Evidence of Effectiveness .....	14
1.3. Benefit-Risk Assessment .....	15
2 Therapeutic Context .....	27
2.1. Analysis of Condition.....	27
2.2. Analysis of Current Treatment Options .....	29
3 Regulatory Background .....	29
3.1. U.S. Regulatory Actions and Marketing History.....	29
3.2. Summary of Presubmission/Submission Regulatory Activity .....	29
3.3. Foreign Regulatory Actions and Marketing History.....	31
4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety.....	32
4.1. Office of Scientific Investigations (OSI) .....	32
4.2. Product Quality .....	34
4.3. Clinical Microbiology.....	34
4.4. Nonclinical Pharmacology/Toxicology .....	34
4.5. Clinical Pharmacology .....	35
4.5.1. Mechanism of Action .....	35
4.5.2. Pharmacodynamics.....	35
4.5.3. Pharmacokinetics.....	36
4.6. Devices and Companion Diagnostic Issues .....	37
4.7. Consumer Study Reviews.....	37
5 Sources of Clinical Data and Review Strategy .....	37
5.1. Table of Clinical Studies .....	37
5.2. Review Strategy.....	42

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

6	Review of Relevant Individual Trials Used to Support Efficacy .....	43
6.1.	Study 2005-01 .....	43
6.1.1.	Study Design.....	43
6.1.2.	Study Results.....	56
6.2.	Study 99-118 .....	84
6.2.1.	Study Design .....	84
6.2.2.	Study Results .....	90
6.3.	CIBMTR Database Study.....	98
6.3.1.	Study Design.....	98
6.3.2.	Study Results.....	100
6.4.	Study 2006-05 .....	107
6.4.1.	Study Design.....	107
6.5.	Study 2004-000592-33 (hereafter Study 2004) .....	119
6.5.1.	Study Design.....	119
6.5.2.	Study Results.....	122
7	Integrated Review of Effectiveness .....	126
7.1.	Assessment of Efficacy Across Trials .....	126
7.1.1.	Primary Endpoints.....	126
7.1.2.	Secondary and Other Endpoints.....	128
7.1.3.	Subpopulations .....	129
7.1.4.	Dose and Dose-Response.....	130
7.1.5.	Onset, Duration, and Durability of Efficacy Effects .....	130
7.2.	Additional Efficacy Considerations .....	130
7.2.1.	Considerations on Benefit in the Postmarket Setting .....	130
7.3.	Integrated Assessment of Effectiveness .....	131
8	Review of Safety .....	138
8.1.	Safety Review Approach .....	138
8.1.1.	Clinical Studies/Trials Used to Evaluate Safety.....	138
8.1.2.	Anticipated Safety Issues .....	138

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

8.1.3. Safety Issues from Other Disciplines .....	139
8.1.4. Review Strategy .....	139
8.2. Review of the Safety Database .....	142
8.2.1. Characteristics of the Safety Population .....	142
8.2.2. Exposure.....	142
8.2.3. Adequacy of the Safety Database.....	143
8.3. Adequacy of Applicant’s Clinical Safety Assessments .....	144
8.3.1. Issues Regarding Data Integrity and Submission Quality .....	144
8.3.2. Categorization of Adverse Events.....	146
8.3.3. Routine Clinical Tests .....	146
8.4. Safety Results .....	147
8.4.1. Deaths .....	147
8.4.2. Serious Adverse Events.....	150
8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects .....	151
8.4.4. Significant Adverse Events .....	152
8.4.5. Treatment Emergent Adverse Events and Adverse Reactions.....	153
8.4.5.1. Common Adverse Events.....	153
8.4.5.2. Dose-Dependency for Adverse Events .....	156
8.4.5.3. Time-Dependency for Adverse Events .....	159
8.4.6. Results of Safety Tests .....	160
8.4.6.1. Laboratory Findings .....	160
8.4.6.2. Vital Signs.....	164
8.4.6.3. Electrocardiograms (ECGs) .....	166
8.4.6.4. QT .....	167
8.4.6.5. Immunogenicity.....	167
8.4.7. Safety in Special Populations .....	168
8.4.7.1. Safety in Pediatric Patients.....	168
8.4.7.2. Safety in Geriatric Patients .....	171
8.4.7.3. Drug-Demographic Interactions .....	171
8.4.7.4. Drug-Disease Interactions .....	172

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

8.4.7.5.	Safety Findings in the Healthy Volunteers .....	173
8.5.	Analysis of Submission-Specific Safety Issues.....	173
8.5.1.	Hemorrhage .....	173
8.5.2.	Hypotension.....	176
8.5.3.	Hypersensitivity Reactions.....	178
8.6.	Specific Safety Studies/Clinical Trials.....	179
8.7.	Additional Safety Explorations.....	179
8.7.1.	Human Carcinogenicity or Tumor Development.....	179
8.7.2.	Human Reproduction and Pregnancy.....	179
8.7.3.	Pediatrics and Assessment of Effects on Growth.....	179
8.7.4.	Overdose, Drug Abuse Potential, Withdrawal, and Rebound .....	180
8.7.5.	Drug-Drug Interactions .....	180
8.8.	Safety in the Postmarket Setting .....	181
8.8.1.	Safety Concerns Identified Through Postmarket Experience.....	181
8.9.	Additional Safety Issues .....	182
8.9.1.	Safety Issues From Other Disciplines.....	182
8.9.2.	Safety Information for Other Sources .....	182
8.9.2.1.	The DF-VOD Trial .....	182
8.9.2.2.	Literature Review .....	184
8.9.2.3.	Studies in Other Indications .....	184
8.9.3.	120-Day Safety Update .....	185
8.10.	Integrated Assessment of Safety .....	186
9	Advisory Committee Meeting and Other External Consultations.....	191
10	Labeling Recommendations .....	191
10.1.	Prescribing Information .....	191
10.2.	Patient Labeling.....	192
10.3.	Nonprescription Labeling.....	192
11	Risk Evaluation and Mitigation Strategies (REMS) .....	193
12	Postmarketing Requirements and Commitments.....	193

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

13 Appendices .....	193
13.1. References.....	193
13.2. Financial Disclosure.....	197

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

### Table of Tables

Table 1 Comparison of the Seattle and Baltimore Criteria for Diagnosis of VOD .....	28
Table 2 Key Development History of Defibrotide.....	30
Table 3 Inspection Results by Site (from Office of Scientific Investigation Summary Review) ....	33
Table 4 Listing of Clinical Trials Relevant to this NDA 208114.....	38
Table 5 Pediatric Patient Enrollment in Clinical Trials .....	41
Table 6 Pediatric enrollment in CIBTMR Registry Trial.....	41
Table 7 Schedule of Assessments for Study 2005-01 .....	51
Table 8 Protocol Amendments For Study 2005-01.....	54
Table 9 Final Disposition for the Historical Control and Defibrotide Group .....	57
Table 10 Description of the Historical Control Groups for Study 2005-01.....	60
Table 11 Exclusion of Groups B and and C from Historical Control.....	61
Table 12 Protocol Violations for Study 2005-01 .....	63
Table 13: Demographic characteristics of the primary efficacy analysis (ITT) .....	64
Table 14 Summary of VOD Diagnosis .....	65
Table 15 Multi-Organ Failure (MOF) Diagnosis .....	66
Table 16 Central Nervous System (CNS) Function at time of VOD Diagnosis .....	67
Table 17 Baseline Transplantation Demographics .....	67
Table 18 Summary of Underlying Disease .....	69
Table 19 Disease Status ITT Analysis Set .....	69
Table 20 Summary of Transplant Type .....	70
Table 21 Conditioning Regimens and GvHD Prophylaxis and Treatment for Study 2005-01 for the ITT Analyses Set .....	70
Table 22 Adult versus Pediatric Patients in Study 2005-01 .....	71
Table 23 Comparison of Demographics between Historical Control Groups A and B versus Defibrotide.....	72
Table 24 Baseline Prognostic Factors between Defibrotide Group and Historical Control Groups A, B and C.....	74
Table 25 Day + 100 post HSCT Survival Rate (Reviewer Table) .....	75
Table 26 Analysis of Survival at Day + 100 using Propensity-Stratified and Weighted Estimate. 76	
Table 27 Day + 100 post-HSCT Survival Rate in Historical Groups (A + B).....	78
Table 28 Nominal P-values from CMH test when comparing Defibrotide cohort vs. historical control cohort B (86 patients).....	78
Table 29 Summary of Subgroup Analyses of Efficacy .....	79
Table 30 Secondary Endpoint of Complete Response Rate .....	81
Table 31 Day + 180 Propensity Weighted Estimate using the Koch Method.....	82
Table 32 Overall Survival Rate .....	82
Table 33 Exposure for Study 2005-01.....	83
Table 34 Schedule of Assessments for Study 99-119 .....	86

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

Table 35 Protocol Amendments for Study 99-118 .....	89
Table 36 Summary of Patient Disposition(All Patients) for Study 99-118.....	91
Table 37 Table of Demographic Characteristics .....	92
Table 38 Summary of VOD Diagnosis and Severity of VOD .....	93
Table 39 Summary of Condition Agent, Graft Type and GVHD Prophylaxis.....	94
Table 40 Complete Response Rate for Study 99-118(Reviewer’s table).....	95
Table 41 Day + 100 post HSCT survival (Reviewer’s table).....	96
Table 42 Defibrotide Exposure for Study 99-118 .....	97
Table 43 Table of Demographic Characteristics .....	102
Table 44 Demographics for CIBMTR Study.....	103
Table 45 Survival at Day + 100 Post-HSCT (Reviewer Table) .....	104
Table 46 Survival at Day + 100 post-HSCT by Age Group (Reviewer Table).....	106
Table 47 Protocol Amendments .....	111
Table 48 Study Populations for Study 2006-05 .....	113
Table 49 Baseline Demographic Variables for Study 2006-05.....	114
Table 50 Baseline Disease Characteristics .....	115
Table 51 Additional Demographic Data for Study 2006-05.....	116
Table 52 Day + 100 Survival post HSCT for Indication Population and ITT Efficacy Population and entire VOD Population .....	118
Table 53 Schedule of Assessments for Study 2004 .....	120
Table 54 Protocol Amendments for Study 2004 .....	122
Table 55 Demographic Characteristics .....	123
Table 56 VOD Diagnosis Day + 30 Primary Endpoint ( FDA Statistical Review Team Table) .....	124
Table 57 Incidence of VOD or Death by Day+30 and Day+100 Post- HSCT .....	125
Table 58 High-Level Description of Studies Supporting Efficacy Claim .....	126
Table 59 Day + 100 Survival post-HSCT across key efficacy studies.....	127
Table 60 Pooled Efficacy Analysis for Study 2005-01, Study 99-118 and 2006-05 .....	128
Table 61 Pediatric Patients enrolled in the key efficacy trials.....	129
Table 62 Pediatric Survival at Day + 100 post HSCT across the 3 trials.....	130
Table 63: Numbers of Patients/Subjects Exposed to Defibrotide .....	140
Table 64: Safety Population – Demographics .....	142
Table 65: SSP - Exposure .....	143
Table 66: Instructions to Investigators for Recording Adverse Events.....	144
Table 67: Safety Population - Deaths.....	147
Table 68: Causes of Death as Report by the Applicant.....	148
Table 69: SSP – Serious Adverse Events by System Organ Class .....	150
Table 70: SSP - Serious Adverse Events by Preferred Term.....	151
Table 71: SSP – TEAE Resulting in Discontinuation.....	152
Table 72: SSP – Common TEAE .....	153
Table 73: SSP – Grades 3 - 5 TEAE.....	155

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

Table 74: SSP – Related TEAE.....	156
Table 75: Study DF-CUP – Summary of Safety Event Rates by Dose .....	157
Table 76: Study DF-CUP – Summary of TEAE by Dose .....	157
Table 77: Study 99-118 – Summary of Safety Event Rates by Dose .....	158
Table 78: Study 99-118 – Summary of TEAE by Dose .....	158
Table 79: NCT 00143546 – Exposure-Adjusted Safety Event Rates by Dose.....	159
Table 80: Pool A – Summary of Safety Event Rates by Duration of Treatment .....	160
Table 81: Key Grades 3 – 4 Laboratory Abnormalities .....	161
Table 82: Study 2005-01 – Vital Sign Outlier Analysis .....	165
Table 83: Study R09-1425 – Time-Averaged Analyses for ECG Intervals .....	166
Table 84: Pool A – Summary of Safety Event Rates Within the Pediatric Cohort By Age .....	169
Table 85: SSP – TEAE By Age Group .....	170
Table 86: Safety Population – Hemorrhage Events .....	174
Table 87: Safety Population – Hypersensitivity Events .....	178
Table 88: SSP – Common Adverse Reactions.....	186

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

### Table of Figures

Figure 1 Enrollment flow chart for the Historical Control Group.....	47
Figure 2 Selection of Historical Control Group .....	59
Figure 3 Time to Event Analysis of Survival at Day + 100 post-HSCT .....	77
Figure 4 Day + 100 post-HSCT Survival for Select Subgroups for the Treatment Group.....	80
Figure 5 CIBMTR Patient Selection .....	101
Figure 6 Kaplan-Meier Probability of Survival at Day + 100 post-HSCT .....	105
Figure 7 Forest plot for 4 studies with Day + 100 survival after transplantation.....	127
Figure 8 Time-to-Event Survival Analysis for Study 2005-01, Study 99-118 and Study 2006-05	132
Figure 9 Survival at Day + 100/Proportion Alive and 95% Confidence Intervals.....	135
Figure 10: Studies 2005-01 and 2004 - Serial Measurements of aPTT.....	163
Figure 11: Vital Signs Following Intravenous Administration of Fraction P .....	177

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

## Glossary

---

AC	advisory committee
ACT	activated clotting time
AE	adverse event
AESI	adverse event of special interest
AML	acute myeloid leukemia
ANC	absolute neutrophil count
ARDS	acute respiratory distress syndrome
ALL	acute lymphoblastic leukemia
ALT	alanine Transaminase
APTT	activated partial thromboplastin time
AST	aspartate Transaminase
AT III	antithrombin III
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
BU	Busulfan
Bu/CY	Busulfan/Cyclophosphamide
CBER	Center for Biologics Evaluation and Research
CBC	complete Blood Count
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CIBMTR	Center for International Blood and Marrow Transplant Research
CICR	cumulative incidence and competing risks
CMC	chemistry, manufacturing, and controls
CMH	Cochran-Mantel-Haenszel
CNS	central nervous system
CR	complete response
CrCl	creatinine clearance
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CTCAE	common terminology criteria for adverse events

## Clinical Review

Tanya Wroblewski, M.D.

Donna Przepiorka, M.D. Ph.D.

NDA 208114

Defitelio (Defibrotide Sodium)

Day + 100	100 Days post Stem Cell Transplant
DFCR	Dana-Farber Cancer Research Institute
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DSMB	Data Safety and Monitoring Board
EBMT	European Society for Blood and Marrow Transplantation
EC	endothelial cell
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCTD	electronic common technical document
EMA	European Medical Agency
ESRD	end stage renal disease
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
GvHD	Graft Versus Host Disease
GFR	Glomerular Filtration Rate
HC	Historical Control
Hgb	hemoglobin
HCT	hematocrit
HIPAA	Health Insurance Portability and Accountability Act
HLA	Human Leukocyte Antigen
HSCT	hematopoietic stem cell transplant
IBMTR	International Bone Marrow Transplant Registry
ICD	informed consent document
ICF	informed consent form
ICH	International Conference on Harmonization
IND	Investigational New Drug
INR	International Normalized Ratio
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
LMWH	low molecular weight heparin
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
MDS	Myelodysplastic Syndrome
mITT	modified intent to treat
MOF	multi-organ failure

## Clinical Review

Tanya Wroblewski, M.D.

Donna Przepiorka, M.D. Ph.D.

NDA 208114

Defitelio (Defibrotide Sodium)

MRC	Medical Research Council
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
NSAIDS	non-steroidal anti-inflammatory drugs
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PAI-1	plasminogen activator inhibitor-1
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
PT	prothrombin time
PTT	partial thromboplastin time
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SIADH	syndrome of Inappropriate Antidiuretic hormone
SMQ	standardized MedDRA query (narrow or broad)
SOC	standard of care, system organ class
SOS	sinusoidal obstructive syndrome
SSP	selected safety population
TBI	Total Body Irradiation
TEAE	treatment emergent adverse event
TEN	toxic epidermal necrolysis
UFH	unfractionated heparin
US	United States
USP	United States Pharmacopeia
VOD	veno-occlusive disease

## 1 Executive Summary

---

### 1.1. Product Introduction

Defibrotide sodium (DEFITELIO) is a polydisperse mixture of predominately single-stranded polydeoxyribonucleotide sodium salts derived from porcine intestinal tissue. Defibrotide sodium demonstrates profibrinolytic properties in vitro but the exact mechanism of action is not fully understood. The recommended indication for defibrotide sodium is for the treatment of adult and pediatric patients with hepatic veno-occlusive disease (VOD) [also known as sinusoidal obstructive syndrome (SOS)] with (b) (4) renal or pulmonary dysfunction. Defibrotide sodium is a new molecular entity (NME). The recommended dosing regimen for defibrotide sodium is 6.25 mg every 6 hours for a minimum of 21 days or until resolution of veno-occlusive disease.

### 1.2. Conclusions on the Substantial Evidence of Effectiveness

The effectiveness of defibrotide sodium is based on efficacy results from the following studies: Study 2005-01 (prospective, historical control study), Study 99-118 (dose-finding study), Study 2006-05 (an expanded access clinical study), and subject level data from the Center for International Blood and Marrow Transplant Research (CIBMTR) registry (Study CIBMTR).

The prospective historically controlled trial (Study 2005-01) enrolled 102 patients in the defibrotide arm and 32 historical controls. All patients had a diagnosis of hepatic VOD with renal or pulmonary dysfunction. Efficacy results in Study 2005-01 evaluated by Day+100 survival after transplantation demonstrated an observed survival rate of 38% (95% CI: 29, 48) in the defibrotide arm compared to 25% (95% CI: 12, 43) in the historical control arm. In the phase 2 dose finding study (Study 99-118), 75 patients with VOD and multi-organ dysfunction who received the recommended defibrotide sodium dose demonstrated a Day + 100 survival of 44% (95% CI: 33, 55). In the expanded access study (Study 2006-05), 351 patients with VOD with multi-organ dysfunction who received the recommended dose of defibrotide sodium showed a Day+100 post-HSCT survival of 45% (95% CI: 40,51). The CIBMTR registry study evaluated 41 subjects with VOD with multi-organ dysfunction at the recommended dose of defibrotide sodium and 55 patients with VOD with multi-organ dysfunction that received standard of care (supportive therapy). The Day+100 survival post-HSCT in the defibrotide sodium arm was 39% (95% CI: 24, 56) compared to the standard of care arm of 31% (95% CI: 19-45).

The Day + 100 survival rates in all four studies are higher than the historical control arm survival

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

(25%), the supportive care arm from the CIBMTR registry study(31%) and published literature (<20%). The totality and consistency of survival at Day + 100 after transplantation provides substantial evidence of efficacy for defibrotide sodium in patients with hepatic veno-occlusive disease with renal or pulmonary failure.

### 1.3. **Benefit-Risk Assessment**

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

### Benefit-Risk Summary and Assessment

Defibrotide sodium is a new molecular entity that is a polydisperse mixture of predominately single-stranded polydeoxyribonucleotides derived from porcine intestinal tissue. The chemical name of defibrotide sodium is polydeoxyribonucleotide, sodium salt. Defibrotide sodium demonstrates profibrinolytic properties in vitro but the exact mechanism of action has not been fully elucidated. The recommended indication for defibrotide sodium is for the treatment of patients with hepatic veno-occlusive disease (VOD), also known as sinusoidal obstruction syndrome (SOS), with (b) (4) renal or pulmonary dysfunction following hematopoietic stem-cell transplantation (HSCT).

Hepatic venous occlusive disease with evidence of multi-organ dysfunction (renal or pulmonary) is a life-threatening condition that can occur after hematopoietic stem cell transplantation. The mortality rate of hepatic VOD with multi-organ dysfunction is over 80% (Coppell et al. 2010). There are currently no approved therapies for the recommended indication, and current standard of care consists of supportive therapy. Despite improvements in supportive care for transplantation over the past decade, the survival for patients with hepatic VOD with multi-organ dysfunction has not improved. There is an unmet medical need for these patients. As a new molecular entity, defibrotide sodium demonstrates an improvement in Day + 100 survival compared with historical controls for patients with hepatic veno-occlusive disease with renal and pulmonary dysfunction. The benefit-risk assessment supports regular approval for the recommended indication.

The demonstration of efficacy of defibrotide is based on the results from four studies: Study 2005-01 (prospective historical control study), Study 99-118 (randomized, Phase 2 dose-finding study), Study 2006-05 (expanded access protocol), and Study CIBMTR (registry study). Study 2005-01, the prospective historically controlled trial, enrolled 102 patients in the defibrotide arm and 32 historical controls. All patients had a diagnosis of hepatic VOD with renal or pulmonary dysfunction. The observed survival at Day+100 after transplantation was 38% (95% CI: 29, 48) in the defibrotide sodium arm. In comparison, the historical control arm Day + 100 survival was 25% (95% CI: 12, 43). Study 99-118 demonstrated a Day + 100 survival post-HSCT of 44% (95% CI: 33, 55) in the 6.25 mg/kg every 6 hours arm. For the indication population in Study 2006-05, the Day + 100 survival post-HSCT was 45% (95% CI: 40, 51). The CIBMTR registry study demonstrated a Day + 100 survival post-HSCT in the defibrotide sodium arm of [39% (95% CI: 24, 56)]. The Day + 100 survival in the CIBMTR registry supportive care arm was [31% (95% CI: 19, 45)].

The Day + 100 survival rates in all four studies are higher than the historical control arm survival (25%), the supportive care arm from the CIBMTR registry study (31%) and from published literature reports (< 20%). The totality and consistency of Day + 100 survival results across the

Clinical Review  
 Tanya Wroblewski, M.D.  
 Donna Przepiorka, M.D. Ph.D.  
 NDA 208114  
 Defitelio (Defibrotide Sodium)

studies provide evidence of effectiveness of defibrotide for the recommended indication.

Defibrotide sodium appears to have reasonable safety profile when assessed in the context of the treatment of a life-threatening disease with no approved therapy options; however, the safety assessment is limited by the lack of complete controlled safety data. There is a high rate of adverse reactions in patients being treated for hepatic VOD with multi-organ dysfunction using the proposed dose-schedule of defibrotide sodium, but there is no consistent signal that any of the events were caused specifically by defibrotide sodium. The published reports of safety of defibrotide sodium in other populations and the review of the postmarket reports are consistent with the relative tolerability of defibrotide sodium in the VOD trials. Hemorrhage, hypersensitivity and pharmacologic interaction with anticoagulants and fibrinolytic therapies are safety concerns that can be mitigated by appropriate warnings, contra-indications and instructions for patient selection and dose modifications in the Prescribing Information. Overall, the clinical benefit of defibrotide sodium remains favorable in light of the residual concern of the lack of a complete safety data from a randomized trial.

The Day + 100 survival after transplantation across the four clinical studies is clinically meaningful given that the survival for this population is expected to be around <20% with supportive care alone. It was not possible to conduct a randomized study that compared defibrotide to a placebo due to the high mortality of disease and ethical considerations. The benefit-risk for defibrotide sodium is positive for the treatment of adult and pediatric patients with hepatic VOD with renal or pulmonary dysfunction. It is this reviewer's recommendation to grant defibrotide sodium regular approval for the following indication: for the treatment of pediatric and adult patients with hepatic veno-occlusive disease (VOD) also known as sinusoidal <sup>(b) (4)</sup> syndrome (SOS) with renal or pulmonary dysfunction.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<a href="#">Analysis of Condition</a>	<ul style="list-style-type: none"> <li>Toxic injury to hepatic endothelial cells from high dose chemotherapy can lead to hepatic veno-occlusive disease (VOD) also known as sinusoidal obstructive syndrome (SOS). The clinical symptoms include painful hepatomegaly, ascites and weight gain.</li> </ul>	<p><b>Hepatic Veno-occlusive disease is a rare condition that most often occurs after hematopoietic stem cell transplantation. Hepatic veno-occlusive disease with multi-</b></p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>Progression and worsening of the occlusion in the terminal hepatic venules can lead to hepatic failure and other organ dysfunction (renal or pulmonary) ultimately leading to death.</p> <ul style="list-style-type: none"> <li>• Most cases of hepatic veno-occlusive disease occur after hematopoietic stem cell transplantation although hepatic VOD can occur after chemotherapy or other toxic insults to the liver.</li> <li>• The incidence of VOD varies between studies due to baseline risk factors, type of transplantation, conditioning regimen and the criteria used for diagnosis. The mean prevalence has been estimated at 14 percent with rates ranging from 5% to as high as 60% (Coppell 2010). A recent literature article reports the incidence to be around 9-13% when using specific diagnostic criteria (Carrerras 2011).</li> <li>• The clinical course can range from mild to moderate to severe. Mild and moderate hepatic VOD often has a self-limiting course. However, hepatic veno-occlusive disease with multi-organ dysfunction is a rare and life-threatening condition with a mortality rate of &gt; 80% (Coppell 2010).</li> </ul>	<p><b>organ dysfunction is a serious and life-threatening medical condition.</b></p> <p><b>Incidence of hepatic VOD varies between studies in the literature. Multi-organ failure and multi-organ dysfunction are used interchangeably in discussions of hepatic VOD. The two organs affected the most frequently in hepatic VOD (outside of the liver) are the pulmonary and renal organs.</b></p> <p><b>The mortality rate of untreated hepatic VOD with multi-organ dysfunction is in excess of 80% (Coppell 2010).</b></p>
<p><a href="#"><u>Current Treatment Options</u></a></p>	<ul style="list-style-type: none"> <li>• There are currently no approved therapeutic agents available for the treatment of hepatic veno-occlusive disease. Treatment usually consists of supportive care.</li> <li>• Despite improvements in supportive care for hematopoietic stem cell transplantation over the past decade, the mortality for patients with hepatic VOD with multi-organ dysfunction has not improved.</li> </ul>	<p><b>There is an unmet medical need for patients for VOD, specifically patients with hepatic VOD with multi-organ dysfunction. This conclusion is based on the high mortality rate (&gt; 80%) for patients with VOD with multi-organ failure and the lack of approved therapy.</b></p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<p><a href="#">Benefit</a></p>	<ul style="list-style-type: none"> <li>Historical control trials are reserved for special circumstances that include diseases with a high predictable mortality when there are too few patients for randomized trials. The use of a historical control trial design is warranted in this special circumstance of hepatic VOD with multi-organ failure with mortality rates in excess of 80% (Coppell 2010) and no available treatment options.</li> <li>Study 2005-01, a multi-center, prospective, open-label, historically controlled trial assessing Day + 100 survival after HSCT of defibrotide at a dose of 6.25 mg/kg every 6 hours administered for a minimum of 21 days or until resolution of VOD. The primary endpoint was Day + 100 survival after HSCT. The high mortality rate for patients with VOD and end-organ failure and the lack of any approved treatment made a historical control the only ethical approach to evaluating the efficacy and safety of defibrotide in this population. The intent-to-treat populations included 102 adult and pediatric patients in the defibrotide treatment arm and 32 adult and pediatric historical control patients.</li> <li>In study 2005-01, at study entry 33% of subjects in the defibrotide arm and 22% in the historical control arm had life-threatening renal or pulmonary dysfunction defined as either dialysis-dependence or requiring mechanical ventilation.</li> <li>In study 2005-01, the efficacy of defibrotide is demonstrated by the observed survival at Day + 100 after HSCT in 25 patients [38% (95% CI 29, <sup>(b)</sup><sub>(4)</sub>)] for the defibrotide arm vs 8 patients [25% (95% CI: 12, 43)] in the historical control. The confidence interval for the</li> </ul>	<p>Hepatic VOD with multi-organ failure has mortality rates in excess of 80% (Coppell 2010) with no available treatment options. This is a special circumstance in which a historical control trial design is acceptable due to the rarity of the disease, high predictable mortality and few patients available for a randomized controlled trial.</p> <p>The high mortality rate for patients with VOD and end-organ failure and the lack of any approved treatment made a historical control the only ethical approach to evaluating the efficacy and safety of defibrotide in this population.</p> <p>The selection of the historical control from the same transplantation centers during the same time frame as the treatment group represents the best available method in this disease setting.</p> <p>All the evidence indicates that the historical control group and the treatment group were well balanced and comparable. The survival in the</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>historical control arm in the label (95% CI: 10, 40) is calculated using asymptotic method.</p> <ul style="list-style-type: none"> <li>Temporally VOD usually occurs prior to Day + 100 post HSCT and usually occurs within the first 30 days post-HSCT. The endpoint of Day + 100 survival post HSCT is a frequently used endpoint for assessing patient survival status following HSCT. While overall survival and survival time points beyond Day+100 are clinically meaningful these survival endpoints may be confounded by underlying disease state and may not adequately capture the effectiveness of defibrotide. Therefore the endpoint of Day + 100 survival post HSCT is the most appropriate endpoint for this disease setting.</li> <li>Source of Historical Control Subjects: The selection of the historical control derived concurrently from same population pool as treatment patients. No prospective trials with sufficient similar populations to use as a historical control. Registry data did not include the necessary patient level data for inclusion in a historical control study.</li> <li>Integrity of the Historical Control Selection Process: The historical control group although small represents a sufficient external group. The Medical Research Committee (MRC) remained blinded and undertook a rigorous review process in selection of historical control. Although 54 out of 86 patients were excluded from the control group resulting in a small final historical control group, an alternate etiology can be ascribed to all 54 patients excluded.</li> </ul>	<p>historical control (75%) is slightly lower than what would be expected based on literature (&gt; 80%, Coppell) and the CIBMTR registry (79%).</p> <p>Only descriptive efficacy results will be presented in the prescribing information [REDACTED] (b) (4)</p> <p>The survival rates at Day + 100 post-HSCT across all four trials are higher than the survival rates in the historical control arm (25%), the CIBMTR registry supportive care arm (31%), and from literature (&lt;20%).</p> <p>The totality and consistency of an improvement in the Day + 100 survival post-HSCT with the use of defibrotide compared to historical controls to include literature reports provides enough weight of evidence to support regular approval of defibrotide sodium for the treatment of patients with hepatic VOD with end-organ</p>

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>The review process by the MRC ensured that the selection of the historical control group was stringent and that only patients with hepatic VOD with end-organ dysfunction were included. The survival in the historical control (75%) is slightly lower than what would be expected based on literature (&gt; 80%, Coppell) and the CIBMTR registry (79%). The historical control represents the best available control group in this setting.</p> <ul style="list-style-type: none"> <li>• <b>Multiplicity:</b> The unplanned sample size adaptations and multiple analyses that occurred during the conduct of trial actually allowed better scrutiny, selection and robustness of the selection of the historical control arm. Survival endpoints are much less subject to bias than response endpoints and the use of a survival endpoint in the study helps to reduce any concerns surrounding the lack of multiplicity adjustment. Additionally, the consistent survival benefit demonstrated across all four of the studies make the statistical concerns regarding the multiplicity issues in the pivotal trial less pertinent.</li> <li>• <b>Analysis Plan not Sufficiently Prespecified:</b> The estimated difference in survival calculated by the Applicant using the propensity-stratified and weighted estimate is 23% with 95% CI (b) (4) with a p-value of (b) (4) by the Koch method. The propensity-stratified estimated difference was prespecified in the SAP, however, the algorithms and ranking methods used for the derivations of the propensity score were not prespecified. Depending upon which strata and algorithm used there can be a wide variation in estimated treatment differences and p-values.</li> </ul>	<p><b>dysfunction.</b></p> <p><b>Based on the demographic and baseline disease characteristics for pediatric and adult patients enrolled across all four studies, the overall population in these studies is comparable to the overall U.S. target population. Therefore, the benefit demonstrated in the pivotal and supportive studies is expected to extend to the post-market setting.</b></p>

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<ul style="list-style-type: none"> <li>• This clinical reviewer acknowledges difficulty in interpretation of the magnitude of the treatment effect depending upon which strata and algorithm used. The totality and consistency of an improvement in the mortality with the use of defibrotide provide enough weight of evidence to support approval of defibrotide sodium for the treatment of patients with hepatic VOD with end-organ dysfunction.</li> <li>• The totality of the survival data across the four studies is paramount in evaluating the efficacy of defibrotide. The consistency and totality of evidence of the improvement on Day + 100 survival post HSCT by defibrotide are not invalidated due to any residual trial design or analyses concerns. Three additional trials support the primary efficacy results of improvement in Day + 100 survival post-HSCT demonstrated in Study 2005-01. These studies include the following: Study 99-118(randomized, Phase 2 dose-finding study), Study 2006-05(expanded access protocol) and Study CIBMTR (Registry study). Study 99-118 demonstrated a Day + 100 survival of 44% (95% CI: 33, 55) in the 25 mg/kg/day arm. For the indication population in Study 2006-05, the Day + 100 survival post-HSCT was 45% (95% CI: 40, 51). The CIBMTR registry study demonstrated an improvement in Day + 100 survival post-HSCT in the defibrotide arm (39%) (95% CI 24-56) compared to the supportive care arm (31%)(95% CI: 19,45). The survival rates at Day + 100 post-HSCT across all four trials are higher than the survival rates in the historical control arm (25%), the CIBMTR registry supportive care arm (31%), and from literature (&lt;20%).</li> </ul>	

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<p><u>Risk</u></p>	<ul style="list-style-type: none"> <li>The safety data for this NDA review included 1894 individuals exposed to defibrotide in seven sponsored studies or trials of treatment of VOD, treatment of other disorders, and prevention of VOD or evaluations of PK or PD. However, none of the trials in patients with VOD collected all treatment emergent adverse events. In order to make the best safety assessment on adverse events of defibrotide at the proposed dose data was pooled from 176 subjects with hepatic VOD and multi-organ dysfunction after HSCT treated with defibrotide 6.25 mg/kg intravenously every 6 hours in Studies 2005-01 and 99-118. This group is the Selected Safety Population (SSP).</li> <li>Mortality within 30 days after the last dose of defibrotide was 55% in the Selected Safety Population and no deaths could be clearly ascribed to defibrotide.</li> <li>The most common (<math>\geq 10\%</math>) SAEs in the SSP were multi-organ failure, hypotension, respiratory failure and renal failure. The most common (<math>\geq 1\%</math>) TEAES resulting in treatment discontinuation were pulmonary hemorrhage, cerebral hemorrhage and sepsis.</li> <li>The most common (<math>\geq 10\%</math>) TEAES in the SSP were hypotension, diarrhea, multi-organ failure, vomiting, renal failure, nausea, epistaxis, respiratory failure, hypertension, hypoxia and pyrexia.</li> <li>In the SSP, Grade <math>\geq 3</math> elevations were reported in 93% for bilirubin and in 27% for creatinine. Additionally, 25% of patients had a grade <math>\geq 3</math> elevation in aPTT but the elevation was not consistent</li> </ul>	<p>Defibrotide appears to have reasonable safety profile when assessed in the context of the treatment of a life-threatening disease with no approved treatment options however the safety assessment is limited by the lack of complete controlled safety data. There is a high rate of adverse reactions in patients being treated for hepatic VOD with multi-organ failure using the proposed dose-schedule of defibrotide but there is no consistent signal that any of the events were caused specifically by defibrotide.</p> <p>Published reports of safety of defibrotide in other populations and review of the postmarket reports are consistent with the relative tolerability of defibrotide in VOD trials. The clinical benefit of defibrotide remains positive in light of the residual concern of the lack of a complete safety data from a randomized trial.</p> <p>The best available adverse event information to assess safety of the proposed dose in the intended population was pooled data from 176 subjects with hepatic VOD and multi-</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>over time with defibrotide use and no dose-dependent increase in PTT was observed in Study 99-118.</p> <ul style="list-style-type: none"> <li>• In a comparative analysis of safety events performed by the Applicant no substantial and consistent adverse effects of defibrotide when used as a treatment or prevention of VOD in the HSCT recipients in comparison to safety outcomes in the respective control groups were observed.</li> <li>• Additional support for the safety of defibrotide comes for two large (&lt; 1000 subjects) trials evaluating the efficacy of defibrotide 200 mg intravenously 4 times day for thromboembolic prophylaxis after surgical procedures. The incidences of adverse reactions reported were &lt;1% and 1.3%.</li> <li>• The safety database does not include sufficient number of subjects (only 1) aged 65 and older to determine whether they respond differently from younger subjects.</li> <li>• Hemorrhage is a clear potential adverse reaction for defibrotide based on its pharmacologic effects and apparent dose-toxicity relationship. Hypersensitivity is a second potential adverse reaction for defibrotide and there were no immunogenicity studies performed.</li> <li>• No formal drug-drug interaction studies were conducted by the applicant. The pharmacological activity of defibrotide suggests it might also be expected to enhance the activity of fibrinolytic agents.</li> <li>• There were no unexpected serious adverse events reported in the</li> </ul>	<p><b>organ dysfunction after HSCT treated with defibrotide 6.25 mg/kg every 6 hours.</b></p> <p><b>The safety analysis of the Selected Safety Population revealed no unexpected events for patients with VOD with multi-organ dysfunction after HSCT.</b></p> <p><b>There were no substantial and consistent adverse effects of defibrotide when used as treatment or prevention of VOD in the HSCT recipients in comparison to safety outcomes in the respective control groups as assessed by the applicant. The additional safety data from two large trials in a thromboembolic prophylaxis indication supports this conclusion.</b></p> <p><b>To ensure that safe use can be recapitulated in practice, the Prescribing Information should contain at least the same levels of controls as the protocols with regard to warnings, patient selection, monitoring, and treatment interruption for bleeding or invasive procedures.</b></p>

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>postmarket setting since the approval of defibrotide in Europe in 2013 for treatments of severe hepatic VOD following HSCT.</p>	<p>Although the incidence of hypersensitive reactions is low, the occurrence of anaphylaxis warrants a warning in the Prescribing information.</p> <p>No important differences are expected in how defibrotide was studied and administered in the clinical trials versus its expected and current use in the post-market setting.</p>
<p><u>Risk Management</u></p>	<ul style="list-style-type: none"> <li>Hemorrhage, hypersensitivity and pharmacologic interaction with anticoagulants and fibrinolytic therapies are safety concerns that can be mitigated by appropriate warnings, contra-indications and instructions for patient selection and dose modifications in the Prescribing Information.</li> <li>The lack of complete safety data from a randomized trial is a residual concern. A safety postmarketing requirement (PMR) is recommended to assess the safety based on the safety results in a randomized, open-label multi-center clinical trial comparing defibrotide versus best supportive care in the prevention of hepatic VOD in adult and pediatric patients, including all adverse events, laboratory abnormalities and frequent peri-infusion vital signs.</li> <li>A PMR is recommended to develop sensitive and specific anti-drug (defibrotide) binding and neutralizing assays and submit the data in a final immunogenicity study report.</li> </ul>	<p>Information in Warnings and Precautions section included in the product labeling adequately address the safety concerns identified during review of this NDA.</p> <p>Two PMRs will be addressed by the Applicant concerning the immunogenicity of defibrotide; milestone dates for the PMRs have been provided by the Applicant.</p> <p>The clinical safety PMR will be addressed by the Applicant in a randomized comparative trial; milestone dates for this study have been provided by the Applicant.</p>

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<ul style="list-style-type: none"><li>• There were no significant safety concerns identified during NDA review requiring risk management beyond labeling or warranting consideration for Risk Evaluation and Mitigation Strategy (REMS).</li></ul>	

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

## 2 Therapeutic Context

---

### Analysis of Condition

Hepatic veno-occlusive disease (VOD) also known as sinusoidal obstructive syndrome (SOS) can occur after toxic injury to the liver and is characterized by the clinical symptoms of jaundice, painful hepatomegaly and fluid retention (Jones RJ 1987 and McDonald GB 1984). The initial case and coining of the term of VOD was reported in 1954 after ingestion of a toxic herbal plant by a patient in Jamaica. The term hepatic veno-occlusive disease was used to describe the obliterative fibrosis in the hepatic venules seen by light microscopy (Bras 1954). After the 1950s with the increasing use of chemotherapy and the advent of transplantation, the occurrence of VOD is now generally seen in patients who undergo hematopoietic stem cell transplantation.

The term sinusoidal obstruction syndrome was proposed in 2002 by DeLeve to replace the term veno-occlusive disease. The rationale for this proposal was based on studies suggesting that the primary site of the toxic injury is the sinusoidal endothelial cells leading to eventual circulatory compromise of the centrilobular hepatocytes, fibrosis and obstruction of liver blood flow. Histological data have not identified the primary site of injury or molecular event that occur in the sinusoids before severe clinical signs of VOD appear. (DeLeve 2002).

Both terms, hepatic VOD and SOS are used in the literature to describe patients undergoing hematopoietic stem cell transplantation who develop the clinical scenario of ascites, weight gain and hepatic failure. For simplicity and purposes of this review the term hepatic VOD will be used rather than SOS as the trials that formed the basis for this review used the term hepatic VOD in the protocols and study descriptions.

The clinical development of hepatic VOD is characterized by tender hepatomegaly, ascites, jaundice and elevation of serum bilirubin in the absence of other etiologies that could cause similar signs and symptoms. The onset of hepatic VOD usually occurs in the early post-transplantation period (within first 1-3 weeks after HSCT) but later presentations can occur. Approximately 50% of patients will develop renal insufficiency and 25% of patients will require hemodialysis. Hepatic VOD with multi-organ failure has a mortality rate of 84% (95% CI: 80%, 89%) within the first 100 days (Coppell 2010, Carreras 2011).

The incidence of VOD varies between studies due to baseline risk factors, type of transplantation, conditioning regimen and the criteria used for diagnosis. The mean prevalence has been estimated at 14 percent with rates ranging from 5% to as high as 60% (Coppell 2010).

There are certain risk factors (pre-transplant characteristics) and factors related to the transplant process are associated with the development of VOD. However the strength of

Clinical Review  
 Tanya Wroblewski, M.D.  
 Donna Przepiorka, M.D. Ph.D.  
 NDA 208114  
 Defitelio (Defibrotide Sodium)

association of each risk factor varies among studies and no one factor or in combination can explain the wide variability in the risk of developing hepatic VOD. The following risk factors are often cited in the literature:

- Preexisting liver disease
- Choice of conditioning regimen (higher with Cytoxan and high doses of radiation)
- Source of graft (allogeneic greater than autologous)
- Patient age (higher in children < 7)
- Poor baseline performance status (PS)

Other risk factors include prior radiation to the abdomen, underlying diagnosis of osteopetrosis, primary HLH or adrenoleukodystrophy.

The diagnosis of hepatic VOD should be entertained in any patient who has undergone HSCT and develops liver dysfunction in the post-HSCT transplant period. The diagnosis of hepatic VOD is usually made on clinical grounds alone in the patient who fulfills either the Seattle or Baltimore criteria. Both diagnostic criteria are used to diagnosis hepatic VOD in clinical practice, but the Seattle criteria are quoted more often in literature for defining the incidence of hepatic VOD. Table 1 describes the two criteria for the diagnosis of VOD.

**Table 1 Comparison of the Seattle and Baltimore Criteria for Diagnosis of VOD**

Seattle Criteria (McDonald, 1984 Hepatology)	Baltimore Criteria (Jones, 1987 Transplantation)
<p>Presence before day 20 after hematopoietic stem cell transplantation (HSCT) of 2 or more of the following:</p> <ul style="list-style-type: none"> <li>• Bilirubin <math>\geq</math> 2mg/dl</li> <li>• Hepatomegaly, right upper the quadrant (RUQ) pain</li> <li>• Ascites +/- unexplained weight gain of &gt; 2% baseline</li> </ul>	<p>Hyperbilirubinemia <math>\geq</math> 2mg/dl before day 21 after HSCT and at least 2 of the following:</p> <ul style="list-style-type: none"> <li>• Hepatomegaly (usually painful)</li> <li>• Ascites</li> <li>• Weight gain <math>\geq</math> 5% from baseline</li> </ul>

Testing should be undertaken to rule out all other potential etiologies such as Budd-Chiari syndrome, acute graft versus host disease, hepatic infections and drug toxicity.

Ultrasonography with Doppler is not diagnostic for hepatic VOD but is often done to rule out extra-hepatic biliary obstruction. A liver biopsy can be diagnostic of hepatic VOD however are often not performed due to concurrent thrombocytopenia and coagulopathy which leads to a substantial risk of bleeding.

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

Clinical criteria have been proposed to define the severity but these criteria are based upon the clinical course and can only be applied retrospectively. A study by McDonald in 1993 designed to help determine the incidence and clinical course of hepatic VOD after HSCT and to analyze risk factors for severe VOD. In general, hepatic VOD can be described as mild, moderate and severe as follows:

- Mild disease- generally require no specific therapy despite elevated liver enzymes
- Moderate disease- generally requires sodium restriction and diuretics for fluid retention and/or medications to alleviate pain for hepatomegaly
- Severe disease- persistent hepatic dysfunction lasting more than 100 days following transplant or died of causes related to hepatic VOD within the first 100 days.

The study demonstrated that survival at Day + 100 was 91% with mild VOD and 77% with moderate disease. Severe VOD has a Day + 100 mortality rate in excess of > 80%.

No therapy for the treatment or prophylaxis of hepatic VOD is approved in the United States. The management of hepatic VOD consists of minimizing potential risk factors and supportive care.

## 2.2. Analysis of Current Treatment Options

There are currently no approved therapies for the treatment or prevention of hepatic veno-occlusive disease. Defibrotide has only been available in the US for hepatic VOD through compassionate use program since 1997.

## 3 Regulatory Background

---

### 3.1. U.S. Regulatory Actions and Marketing History

Defibrotide is a new molecular entity (NME) and is not currently marketed in the U.S.

### 3.2. Summary of Presubmission/Submission Regulatory Activity

NDA 208114 was received on 31 July 2015 as an electronic submission in eCTD format. The contents of the clinical module were reviewable and the application was filed on September 29, 2015. A priority review designation was granted.

The regulatory history of defibrotide is long and the following table provides a brief snapshot of the key regulatory interactions between the Agency and the Applicant.

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

**Table 2 Key Development History of Defibrotide**

1980s	Defibrotide was produced in 1983, and oral and injectable formulations developed by Gentium S.p.A. (formerly Crinos-Villa Guardia [Como]-Italy) received marketing authorization (MA) in Italy for prophylaxis of deep-vein thrombosis and treatment of thrombophlebitis (Proclide <sup>®</sup> , Noravid <sup>®</sup> ).
2000	Phase 2 dose-finding study to treat severe VOD (99-118) enrolled its first patient.
2003	Gentium submitted US IND 62118 for defibrotide to treat severe hepatic VOD.
2009	Italian marketing authorizations for all defibrotide products were withdrawn by Gentium S.p.A. effective April 2009 for commercial reasons.
2009	Pivotal Phase 3 Study in the US for the treatment of hepatic VOD (b) (4) completed.
2011	Gentium submitted NDA (b) (4) however FDA identified issues related to the clinical data in application and Gentium withdrew application in August.
2013	Defibrotide (trade name Defitelio <sup>®</sup> ) was granted Marketing authorization by the European Commission for the treatment of severe hepatic veno-occlusive disease (VOD) also known as sinusoidal obstructive syndrome (SOS) in hematopoietic stem cell transplantation (HSCT) therapy.
2014	Gentium was acquired by Jazz Pharmaceuticals. Meetings with the FDA established a path forward for defibrotide development in the US and agreed on the content of a new application. FDA granted rolling review of this NDA in November 2014.
2015	Defibrotide was granted marketing authorization in Israel.
2015	The complete NDA 208114 was submitted to the FDA (July 31, 2015).

The key points in the development history include the following:

- Jazz Pharmaceuticals (formerly Gentium S.p.A) was granted orphan designation for defibrotide for the treatment of hepatic VOD on 21 May 2003.
- IND 62118 (Commercial IND) was submitted to the Agency on 15 December 2003. The Applicant initiated the Phase 3 pivotal study (2005-01) under IND 62118 enrolling the first patient in July 2006.
- In January 2014, Gentium became a Jazz Pharmaceutical company. In April 2014, Jazz Pharmaceutical clinical and regulatory teams had a Type A meeting with the FDA and a path forward was agreed upon. Following that meeting, the Applicant met with the Agency in 2014 and the Agency granted a rolling review for the NDA with the first module submitted in March 2015.

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

- The complete NDA 208114 was submitted on July 31, 2015.
- This NDA was granted a priority review at the time of the filing review (September 29, 2015)

### 3.3. **Foreign Regulatory Actions and Marketing History**

Defibrotide was originally approved and marketed as Procidide® and Noravid® in Italy in 1986 for the prophylaxis of deep vein thrombosis and the treatment of thrombophlebitis. In 2009, for business reasons and to focus on the clinical development program for the treatment and prevention of hepatic VOD, the Italian marketing authorizations were withdrawn by the Applicant. The original manufacturer of defibrotide was Gentium S.p.A (formally Crinos-Villa Guarda [COMO]) based in Italy and in January 2014, Gentium became a Jazz Pharmaceutical company.

In May 2011 the European Medical Agency (EMA) received an application for defibrotide for a treatment and prevention indication for hepatic VOD. Between 2011 and 2013 several outstanding issues raised by the Committee for Medicinal Products for Human Use (CHMP) were addressed by the Applicant in written responses and oral explanations. During the March 2013 CHMP meeting, the Committee issued a negative scientific opinion for defibrotide in light of the overall data submitted.

A request for re-examination was submitted to the EMA in April 2013 by the Applicant. The re-examination procedure commenced in June 2013 and included expert opinion, the joint assessment report on the applicant's detailed grounds for re-examination, and an oral explanation by the Applicant. During the CHMP meeting in July 2013, the Committee, in light of the scientific data available, re-examined the initial opinion of defibrotide. The Committee's final opinion concluded that the applicant satisfied the criteria for authorization and recommended the granting of marketing authorization for defibrotide for the treatment indication under exceptional circumstances. In October 2013, the European Commission granted a marketing authorization for defibrotide under the trade name Defitelio® for the treatment of severe hepatic VOD also known as SOS in HSCT therapy under exceptional circumstances.

Defibrotide was granted marketing authorization in Israel in 2015 under the same trade name for the same indication. Defibrotide has only been available in the US through compassionate use programs since 1997.

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

## **4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety**

---

### **4.1. Office of Scientific Investigations (OSI)**

For full details, see the Clinical Inspection Summary by Dr. Orenca. Three clinical sites were selected and the rationale is provided below.

The Applicant conducted Study 2005-01 at 35 sites with all but six sites in the US (Canada and Israel). There were a total of 102 patients in the treatment group and 32 patients in the final historical control group. The initial screening for the historical control group included over 6000 charts and was eventually narrowed down during the Medical Review Committee (MRC) selection process to 32 charts for review. These charts and data will not be available for site inspections and only the 102 treatment group patient's charts will be available for inspection.

Site inspections occurred at the three sites in the United States that enrolled the most patients into the treatment group arm of Study 2006-05. Given the amount of missing data (laboratory, clinical parameters) with the initial NDA submission we felt a thorough site inspection of the three sites that enrolled the most subjects will be the most valuable to our review process.

The three sites selected were chosen based on the total number of patients enrolled and critical and minor protocol violations. Critical protocol violations included the following: inclusion/exclusion criteria, informed consent documentation, concomitant medications and study drug deviations. The adherence to the inclusion and exclusion criteria in the treatment group is critical to ensure equipoise between the historical control group and treatment group. Minor protocol deviations include laboratory, daily weights and physical exam findings not recorded at proper time intervals or not completed at all. While these violations are termed minor these measurements are used to help determine complete remission of VOD as the secondary endpoint. A high degree of missing data may call into question the validity of the second endpoint and the study in general.

Site 01(Dana-Farber Cancer Institute) enrolled the largest number of patients (13) followed by Site 11(University of Minnesota Medical Center) (11) and lastly by site 08(Memorial Sloan Kettering) with 8 subjects. Site 11 and Site 08 had several critical protocol violations. Site 01 had fewer critical protocol violations but had numerous minor protocol violations to include laboratory and daily weights not performed on time.

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

**Table 3 Inspection Results by Site (from Office of Scientific Investigation Summary Review)**

<b>Name of CI Location</b>	<b>Study Site/Protocol 2005-01/Number of Subjects Enrolled (n)</b>	<b>Inspection Date</b>	<b>Classification*</b>
Paul Richardson, MD Dana-Farber Cancer Institute 44 Binney Street Boston, MA 02215	Site #01  Subjects= 13 (treatment group)	November 6-12, 2015	Preliminary: NAI
Angela Smith MD, MS University of Minnesota Medical Center 500 Harvard Street Minneapolis, MN 55455	Site #11  Subjects= 11 (treatment group)	October 13-28, 2015	Preliminary: VAI
Nancy Kernan, MD Memorial Sloan-Kettering Cancer Center 1275 York Ave New York, NY 10065	Site #08  Subjects= 8 (treatment group)	October 28-November 4, 2015	Preliminary: NAI
Jazz Pharmaceuticals 3180 Porter Drive Palo Alto, CA 94304	Sponsor of Study Protocol 2005-01	January 12-22, 2015	Pending

**\*Key to Classifications**

NAI = No deviation from regulations. Data acceptable.

VAI-No Response Requested = Deviations(s) from regulations. Data acceptable.

OAI = Significant deviations from regulations. Data unreliable/critical findings may affect data integrity.

Preliminary=The Establishment Inspection Report (EIR) has not been received, findings are based on preliminary communication with the field at the Office of Regulatory Affairs (ORA), or final review of the EIR is pending.

Once a final letter is issued by CDER to the inspected entity and the case file is closed, the preliminary designation is converted to a final regulatory classification.

The preliminary classification for Dr. Richardson and Dr. Kernan is No Action Indicated (NAI). The preliminary classification for Dr. Smith is Voluntary Action Indicated (VAI). The regulatory issues noted at the Dr. Smith site include late serious adverse event reporting and incorrect drug dosing calculations.

*Reviewer Comment: The clinical review team discussed the findings of site 11 with Office of Scientific Investigations. All SAEs were eventually reported to the Agency and given frequent adaptations to the trial and iterative submissions of study protocol, delay in SAE reporting unlikely to impact overall assessment of efficacy for this study. The incorrect dosing calculations resulting in an increase in cumulative doses of defibrotide sodium are not considered major violations and unlikely to impact overall assessment of efficacy for this study.*

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

#### 4.2. **Product Quality**

The chemical name of defibrotide is polydeoxyribonucleotide sodium salt and has a mean molecular weight of 13-20kDA and potency of 27-39 biological units per mg. Defibrotide injection is a clear, light yellow to brown, sterile, preservative-free solution for intravenous use. Each millimeter of the injection contains (b) (4) mg of defibrotide and 10 mg of sodium citrate, USP, in water for Injection, USP. Hydrochloric acid, NF, and/or sodium hydroxide, NF, may have been used to adjust pH to 6.8-7.8. Each (b) (4) mg of defibrotide is equivalent to 80 mg of defibrotide sodium salt.

The USP <1121> Salt Policy stipulates that USP will base the strength of the drug product on the active moiety. (b) (4)

(b) (4)  
(b) (4)  
(b) (4)  
(b) (4) The recommended dose of defibrotide sodium is 6.25 mg/kg. Refer to the CMC review by the Quality Review Team for full details.

#### Immunogenicity

The potential immunogenicity of the product was not evaluated in the NDA. The reviewers conclude that this immunogenicity deficiency be addressed as a post marketing commitment (PMC).

For further details, refer to the CMC review by the Quality Review Team.

#### 4.3. **Clinical Microbiology**

Refer to CMC review; there were no Clinical Microbiology concerns.

#### 4.4. **Nonclinical Pharmacology/Toxicology**

##### Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity studies have been conducted with intravenous administration of defibrotide. Defibrotide was not mutagenic *in vitro* in a bacterial reverse mutation assay (Ames assay). Defibrotide was also not clastogenic in either an *in vitro* chromosomal aberrations assay in

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

Chinese hamster ovary cells or an *in vivo* micronucleus assay conducted in bone marrow cells from rats administered defibrotide by intravenous infusion.

Animal Toxicology and/or Pharmacology

For complete review, See Pharmacology/Toxicology review from current NDA submission by Brenda Gehrke Ph.D. and Christopher Sheth Ph.D.

#### 4.5. **Clinical Pharmacology**

For full details, see the clinical pharmacology review from current submission by Guixiang Shen Ph.D. and Bahru A. Habtemariam Pharm.D.

##### 4.5.1. **Mechanism of Action**

The mechanism of action of defibrotide has not been fully elucidated. Studies evaluating the pharmacological effects of defibrotide on endothelial cells (EC) were conducted primarily in the human microvascular endothelial cell line. *In vitro*, defibrotide increased tissue plasminogen activator (t-PA) and thrombomodulin expression, and decreased von Willebrand factor (vWF) and plasminogen activator inhibitor-1 (PAI-1) expression, thereby reducing EC activation and increasing EC-mediated fibrinolysis. Defibrotide protected ECs from damage caused by chemotherapy, tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), serum starvation, and perfusion. *In vitro*, defibrotide enhances the enzymatic activity of plasmin to hydrolyze fibrin clots.

##### 4.5.2. **Pharmacodynamics**

At a dose 2.4 times the maximum recommended dose, defibrotide, does not prolong the QTc interval to any clinically relevant extent.

Plasma concentrations of PAI-1 were assessed on an exploratory basis as a potential pharmacodynamics marker for efficacy in Study 99-118. PAI-1 is an inhibitor of t-PA and therefore of fibrinolysis. Mean PAI-1 levels on Days 7 and 14 were lower than those at baseline in patients with complete response (CR) and in those who were alive at Day+100, but this trend did not reach statistical significance. There were no statistically significant differences in mean PAI-1 levels by treatment or outcome.

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

### 4.5.3. Pharmacokinetics

#### *Absorption*

After intravenous administration, peak plasma concentrations of defibrotide occur approximately at the end of each infusion.

#### *Distribution*

Defibrotide is highly bound to human plasma proteins (average 93%) and has a volume of distribution of 8.1 to 9.1 L.

#### *Elimination*

Metabolism followed by urinary excretion is likely the main route of elimination. The estimated total clearance was 3.4 to 6.1 L/h. The elimination half-life of defibrotide is less than 2 hours. Similar plasma concentration profiles were observed in VOD patients after initial and multiple-dose administration of 6.25 mg/kg every 6 hours for 5 days. Therefore, no accumulation is expected following multiple-dose administration.

#### Metabolism

Though the precise pathway of defibrotide degradation in plasma *in vivo* is largely unknown, it has been suggested that nucleases, nucleotidases, nucleosides, deaminases, and phosphorylases metabolize polynucleotides progressively to oligonucleotides, nucleotides, nucleosides, and then to the free 2'-deoxyribose sugar, purine and pyrimidine bases.

The biotransformation of defibrotide was investigated *in vitro* by incubation with human hepatocytes from donors of different ages and showed that defibrotide does not undergo appreciable metabolism by human hepatocyte cells.

#### Excretion

After administration of 6.25 mg/kg to (b) (4) mg/kg doses of defibrotide as 2-hour infusions, approximately 5-15% of the total dose was excreted in urine as defibrotide, with the majority excreted during the first 4 hours.

#### *Specific Populations*

##### Age: Pediatric Population

Insufficient PK data were collected in pediatric patients to draw conclusions.

##### Renal Impairment

The safety, tolerability, and pharmacokinetics of 6.25 mg/kg as 2-hour intravenous infusions of defibrotide were evaluated in patients with Hemodialysis-dependent End Stage Renal Disease (ESRD) during hemodialysis and on days off dialysis, and in patients with severe renal disease or ESRD not requiring dialysis. Defibrotide was not removed by hemodialysis, which had no notable effect on plasma clearance of defibrotide. Terminal half-lives were consistently less

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

than 2 hours, and there was no accumulation of defibrotide following repeated dosing. Defibrotide exposure (AUC) in patients with severe renal impairment or ESRD was 50% to 60% higher than that observed in matched healthy subjects. Peak concentration (C<sub>max</sub>) was 35% to 37% higher following single- and multiple-dose administration of defibrotide.

#### Drug Interactions

Pharmacokinetic drug-drug interactions are unlikely at therapeutic dose. Data from *in vitro* studies using human biomaterial demonstrate that defibrotide does not induce (CYP1A2, CYP2B6, CYP3A4, UGT1A1) or inhibit (CYP1A2, CYP2B6, CYP3A4, CYP2C8, CYP2C9, CYP2C19, CYP2D6, UGT1A1, UGT2B7) the major drug metabolizing enzymes and is not a substrate or inhibitor of the major drug uptake transporters (OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3) or efflux transporters (P-gp and BCRP).

#### **4.6. Devices and Companion Diagnostic Issues**

Not applicable.

#### **4.7. Consumer Study Reviews**

The Division of Medication Error Prevention and Analysis reviewed the proposed Prescribing Information and the proposed carton and vial labels. They identified improvements to increase the readability, promote safe use of the product and mitigate confusion.

## **5 Sources of Clinical Data and Review Strategy**

---

### **5.1. Table of Clinical Studies**

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

**Table 4 Listing of Clinical Trials Relevant to this NDA 208114**

<b>Trial Identity</b>	<b>Trial Design</b>	<b>Regimen/schedule/route</b>	<b>Study Endpoints</b>	<b>Treatment Duration/Follow Up</b>	<b>No. of patients enrolled</b>	<b>Study Population</b>	<b>No. of Centers and Countries</b>
<b><i>Controlled Studies to Support Efficacy and Safety</i></b>							
2005-01	Phase 3, multi-center, open-label, historical control Study	25 mg/kg/day in 4 divided doses each over 2 hours	Primary: Day + 100 survival Secondary: Day + 100 CR, Day + 180 survival, OS	Median duration: 22 days	134 total 102- defibrotide arm 32- Historical Control	Adult and Pediatric patients with post-HSCT Severe VOD(VOD with MOF)	34 US and International sites Canada Israel
99-118	Investigator initiated phase 2, multi-center, randomized, open-label	25 mg/kg versus 40 mg/kg	Primary: CR rate by Day + 100 Secondary: Day + 100 survival	Median duration: 14 days	149 total 75:Defibrotide (25 mg/kg/day) 74: Defibrotide (40 mg/kg/day)	Adult and Pediatric Patients with VOD following HSCT with organ dysfunction or at high risk to develop VOD	9 sites(US only)
Study 2006-05	Ongoing U.S. expanded access treatment for the open-label treatment of patients with VOD	25 mg/kg/day in 4 divided doses each over 2 hours	Day +100 survival, Complete Response by Day + 100	Median duration: 20 days	681 patients enrolled as of 31 Dec 2013 ITT Efficacy Population: VOD with MOF: 351 HSCT patients	Adult and pediatric patients post HSCT or post chemotherapy with VOD	78 sites(US only)

Clinical Review

Tanya Wroblewski, M.D.

Donna Przepiorka, M.D. Ph.D.

NDA 208114

Defitelio (Defibrotide Sodium)

<b>Trial Identity</b>	<b>Trial Design</b>	<b>Regimen/ schedule/ route</b>	<b>Study Endpoints</b>	<b>Treatment Duration/ Follow Up</b>	<b>No. of patients enrolled</b>	<b>Study Population</b>	<b>No. of Centers and Countries</b>
CIBMTR	Registry Database for HSCT recipients	Information not recorded	Day + 100 survival (binary outcome), OS, VOD resolution by Day + 100	Unknown	96 patients(41 treated with defibrotide and 55 not treated with defibrotide	Hepatic VOD with selected parameters of renal and/or pulmonary dysfunction post-HSCT	54 US Centers
Study 2004-000592-33	Phase 3, multi-center, randomized, open-label, Controlled study for prophylactic use of defibrotide for prevention of HST	25 mg/kg/day	Incidence of VOD by Day + 30, MOF by Day + 100 survival for subjects with VOD, Day + 180 survival for subjects with VOD	From Conditioning up to day + 30 for prophylaxis, continuing or crossing over to defibrotide treatment upon VOD diagnosis	356 randomized and included in ITT analyses set(180 defibrotide prophylaxis, 176 control/best supportive care	Pediatric patients undergoing myeloablative therapy and HSCT at high risk for VOD	28(US and International) 26 sites in European Economic Area and 1 site in Switzerland and 1 site in Israel
<b><i>Additional Studies to Support Safety</i></b>							
Study DF-CUP	International compassionate use program in the US and EU that provides defibrotide for the treatment of patients with hepatic VOD	10-80 mg/kg/day	Day + 100 survival	Minimum of 14 days	710 patients enrolled(1129 patients received defibrotide but voluntary efficacy data	Hepatic VOD with or without MOF post-HSCT or chemotherapy	231 International) 26 sites in European Economic Area and 1 site in Switzerland

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

<b>Trial Identity</b>	<b>Trial Design</b>	<b>Regimen/ schedule/ route</b>	<b>Study Endpoints</b>	<b>Treatment Duration/ Follow Up</b>	<b>No. of patients enrolled</b>	<b>Study Population</b>	<b>No. of Centers and Countries</b>
					provided for 710 patients)		and 1 site in Israel
<b><i>Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)</i></b>							
R09-1425	Phase I, single-centers safety pharmacology study to assess effect of defibrotide on the QTc	6.25 mg/kg and supratherapeutic (15 mg/kg)	Thorough QT study	Single dose delivered over 2 hour infusion	52 patients	Healthy adult volunteers	1(US)
-Study DF VOD-2012-03-PKRen	Phase 1 study to evaluate defibrotide in patients with renal impairment	Main Study: defibrotide 25 mg/kg/day, Dialysis study: Defibrotide 6.25 mg/kg on non-dialysis day and dialysis day(Day 4)	PK Study	Main Study- 1 day Dialysis Study: 2 days	Main study- severe ESRD- 6 healthy subjects, Dialysis Study: 6 subjects	ESRD on dialysis Patients with severe ESRD not on dialysis and healthy volunteers	2(US)
Study DFPL99-118	Characterized PK of defibrotide in subset of patients from Study 99-118 with VOD with evidence of multi-organ failure	Defibrotide 10 mg/kg/day in 4 divided dose on day 1 then 25 mg/kg day in 4 divided doses and also 40 mg/kg/day	PK in patients with VOD with evidence of MOF who receive either 25 mg/kg/day or 40 mg/kg day of defibrotide	Minimum of 14 days	11 subjects	VOD following HSCT by Baltimore Criteria with evidence of MOF	9(US) in main Study

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

The clinical trials submitted in support of this NDA enrolled pediatric patients. The following table describes the number of pediatric patients enrolled in the pivotal trial 2005-01 as well as the key supportive trials 99-118 and 2006-05. The CIBMTR registry study is discussed separately below with regard to pediatric enrollment.

**Table 5 Pediatric Patient Enrollment in Clinical Trials**

	Study 2005-01		Study 99-118		Study 2006-05
	Defibrotide N=102	HC N=32	25 mg/kg N=75	40 mg/kg N=74	N=351*
Subjects ≤16 years of age n(%)	44(43)	14(44)	22(29)	23(31)	189(53)

HC- historical control

\*includes only indication population from Study 2006-05

The CIBMTR registry study also included pediatric subjects. The following table provides the summary of pediatric patients who were < 16 years of age compared to those who were greater than or equal to 16 years of age.

**Table 6 Pediatric enrollment in CIBTMR Registry Trial**

Variable	Defibrotide N=41 n(%)	Non-defibrotide N=55 n(%)
< 16 years	25(61)	11(20)
≥ 16 years	16(39)	44(80)

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

## 5.2. Review Strategy

The key materials used for the review of efficacy and safety includes:

- NDA 208114 datasets(raw and derived), clinical study reports, and responses to the review team’s information requests
- Relevant published literature
- Relevant information in the public domain
- Periodic Safety Update Reviews(PSURs)

The efficacy review was conducted by Tanya Wroblewski, M.D. and the safety review was performed by Donna Przepiorka, M.D., Ph.D. Sections 1-7 and 9-13 of the review were written by Tanya Wroblewski, M.D. and Section 8 was written by Donna Przepiorka, M.D., Ph.D. The statistical review was conducted by Yuan-Li Shen, Ph.D. and Xin Gao, Ph.D.

The drug product and proposed dose is defibrotide sodium 6.25 mg every 6 hours. Throughout this review the term defibrotide refers to defibrotide sodium.

This review was primarily based on analysis of Study 2005-01 and Study 99-118. Additional studies were used to support the efficacy data included CIBMTR Registry Study and Study 2006-05. Additional efficacy data from Study 2004 submitted by the Applicant was reviewed and verified. Data from all of the studies listed in Table 4 formed the basis for the analysis of safety.

Using the primary data from the pivotal study and supportive efficacy studies, the statistician confirmed and in collaboration with the clinical reviewer, supplemented the Applicant’s efficacy analyses. Statistical analyses by the efficacy reviewer were performed using JMP 10.0(SAS Institute, INC., Cary NC) and JMP Clinical. For the results of the primary efficacy analysis provided by the statistician, refer to the Statistical Review by Cindy Gao Ph.D. and Yuan-Li Shen Ph. D. Unless specifically referenced, all analyses and presentation of findings are the work of FDA reviewers.

*Reviewer Comment: The indication for defibrotide is for patients with hepatic VOD with (b) (4) renal or pulmonary dysfunction. Enrollment into the pivotal and supportive trials required evidence of multi-organ failure (demonstrated by renal/pulmonary dysfunction). The terms multi-organ dysfunction (MOF) and multi-organ dysfunction are used synonymously throughout this review.*

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

## **6 Review of Relevant Individual Trials Used to Support Efficacy**

---

### **6.1. Study 2005-01**

#### **Study Design**

##### **Overview and Objective**

Study 2005-01 is entitled, “Defibrotide for the Treatment of Severe Hepatic Veno-Occlusive Disease in Hematopoietic Stem Cell Transplant (HSCT) Patients: A Historically-Controlled, Multi-center Phase 3 Study to Determine Safety and Efficacy.” The primary objective of Study 2005-01 is to demonstrate the efficacy of defibrotide in patients with severe VOD (hepatic VOD with MOF) in terms of survival at day + 100 post-HSCT in patients who received defibrotide(defibrotide group) compared to the final historical control group.

The key secondary objectives include the following:

- To compare the complete response(CR) rate by Day + 100 post-HST in the defibrotide versus historical control groups
- To compare survival at Day + 180 post-HSCT in the defibrotide versus the historical control groups
- To compare overall survival(defined as mortality status at the date of last contact) post-HSCT in the defibrotide versus the historical control groups
- To assess the safety of the selected dose and schedule
- To collect and bank samples prior to and during therapy for special studies of potential serum and endothelial markers for VOD.

*Reviewer Comment: For the purposes of this review the term severe VOD and hepatic VOD with multi-organ failure are synonymous.*

##### **Trial Design**

Study 2005-01 is a historically-controlled, multicenter, open-label phase 3 study to determine the safety and efficacy of 25 mg/kg/day of defibrotide for the treatment of severe VOD in patients undergoing HSCT.

Eligible subjects included those who met the Baltimore diagnostic criteria for VOD by Day + 21 post-HSCT. In addition, subjects must also fulfill the criteria for multi-organ failure (MOF) (pulmonary and/or renal dysfunction).

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

Defibrotide will be dosed at 6.25 mg/kg every 6 hours with a total daily dose of 25 mg/kg. Defibrotide will be administered for a minimum of 21 days. Treatment will be continued as circumstances allow or until the patient is discharged from the hospital. Defibrotide administration may be held for toxicity or delayed for necessary medical/surgical interventions.

Patients will be placed into the following stratification categories: ventilator and/or dialyses dependent,  $\leq 16$  years of age, allogenic transplant, and prior stem cell transplant.

#### Historical Control Group

Study 2005-01 examines the efficacy and safety of defibrotide 25 mg/kg /day in patients with severe VOD using a historical control group as the comparator. Given that severe VOD is associated with a very high mortality rate (80% mortality past Day + 100) and no effective treatment exists, no prospective controls are feasible. Thus the only ethical feasible approach to evaluate defibrotide in a severely ill population was the choice of a historical control.

*Reviewer Comment: The Applicant attempted to conduct an earlier controlled study in the treatment indication but the trial was terminated after 3 years due to low accrual rates. This low accrual rate was likely due to the more frequent use of defibrotide by clinical centers and the availability of the drug on compassionate use basis. The Applicant then explored the feasibility of conducting Study 2005-01 as a controlled, blinded randomized study in the US. The Applicant contacted 12 of the largest stem cell institutions in the US and based upon the responses from the investigators at these 12 institutions, it was felt that a controlled, blinded and randomized trial in current indication would be unethical due to the high mortality rates that are seen in patients with severe hepatic VOD. Thus a historical control group was chosen for study 2005-01.*

#### Key Inclusion/Exclusion Criteria

Patients must meet both of the following criteria to be enrolled in the treatment and historical control groups:

1. Clinical Diagnosis of VOD: Defined by jaundice (bilirubin  $\geq 2$ mg/dl) and at least 2 of the following clinical findings, by Day + 21 post stem cell transplant:
  - Ascites
  - Weight gain  $\geq 5\%$  above baseline weight (defined as weight on the first day of conditioning- if this value was not available, the weight on the date of admission the HSCT unit may have been used).
  - Hepatomegaly, patients with pre-existing hepatomegaly must have had documentation by physical exam or imaging that liver size is increased over baseline (at the time of admission for HSCT)

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

2. Severe VOD: Defined as VOD with MOF (i.e. presence of one or both of the following, by Day + 28 post-HSCT):
  - Renal dysfunction: a) serum creatinine  $\geq 3 \times$  value on the date of admission to the HSCT unit for conditioning or  $\geq 3 \times$  lowest value during condition prior to HSCT(whichever was lowest) or b) creatinine clearance of  $GFR \leq 40\%$  of admission value or c) dialysis dependence
  - Pulmonary dysfunction: documentation of oxygen saturation  $\leq 90\%$  on room air (2 consecutive measurements at least one hour apart). If it was not possible to obtain a second oxygen saturation measurement on room air without jeopardizing the patient's safety, a single measurement of  $\leq 90\%$  was considered to be sufficient, or requirement for oxygen supplementation/ventilator dependence. Dysfunction must have been attributable to fluid overload or mechanical impingement from abdominal distention or hepatic enlargement and not to an infectious cause.

Exclusion Criteria: The criterion for exclusion were similar for both groups with the exception of exclusion of patients from the treatment group based on known risk factors associated with defibrotide which would not have been applicable to the historical control group.

#### Exclusion Criteria

- Documentation of pre-existing(at time of HSCT) cirrhosis of the liver
- An alternative diagnosis for ascites, weight gain, and jaundice such as viral hepatitis, at the time that severe VOD criteria were met.
- Documented diagnoses of GvHD, grade B-D according to the International Blood Marrow Transplant Registry (IBMTR) Severity Index, involving the liver or gut, or documented diagnosis of GvHD, grade C or higher according to the IBMTR Severity Index, involving skin.
- Patients with grade B GvHD involving skin only were eligible. Grade was established without consensus grading for the purpose of this study.
- Prior solid organ transplant
- Dependence on dialysis on admission, prior to and/or time of HSCT, or oxygen dependence during conditioning prior to HSSCT
- Use of any medication which increased the risk of hemorrhage. Use of heparin or other anticoagulation within 12 hours unless being used for routine central venous line management, fibrinolytic instillation for central venous line occlusion, intermittent dialysis or ultrafiltration of continuous veno-venous hemofiltration.
- Clinically significant uncontrolled acute bleeding, defined as hemorrhage requiring  $< 15\text{cc/kg}$  of packed red blood cells to replace blood loss, or bleeding from a site which in the Investigator's opinion constituted a potential life-threatening source, irrespective of

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

amount of blood loss at any time point from the date of HSCT through the date of severe VOD diagnosis.

- Hemodynamic instability as defined by a requirement for multiple vasopressors or inability to maintain mean arterial pressure with single vasopressor support.

For patients with concurrent or confounding causes of liver dysfunction clinically evident or evident on ultrasound or other radiographic imaging or by medial assessment per institutional practice, biopsy, and or wedged hepatic venous pressure measurements should have been obtained as necessary to rule out the conditioning exclusions above.

#### Selection Process of the Final Historical Control Group

There was a pre-specified detailed methodology for the process by which the Historical Control group was screened and ultimately selected by the Medical Review Committee (MRC). The process was supplemented by a Medical Review Committee Standard Operating Procedure.

First pass screening was conducted by indecent patient screeners who scored charts of possible Historical Control patients and provided the charts of potentially eligible patients to the MRC for review. Sites from which potential patients were selected were broadly categorized into 2 groups depending on who would be assigned as the HSCT Screener and Primary Reviewer:

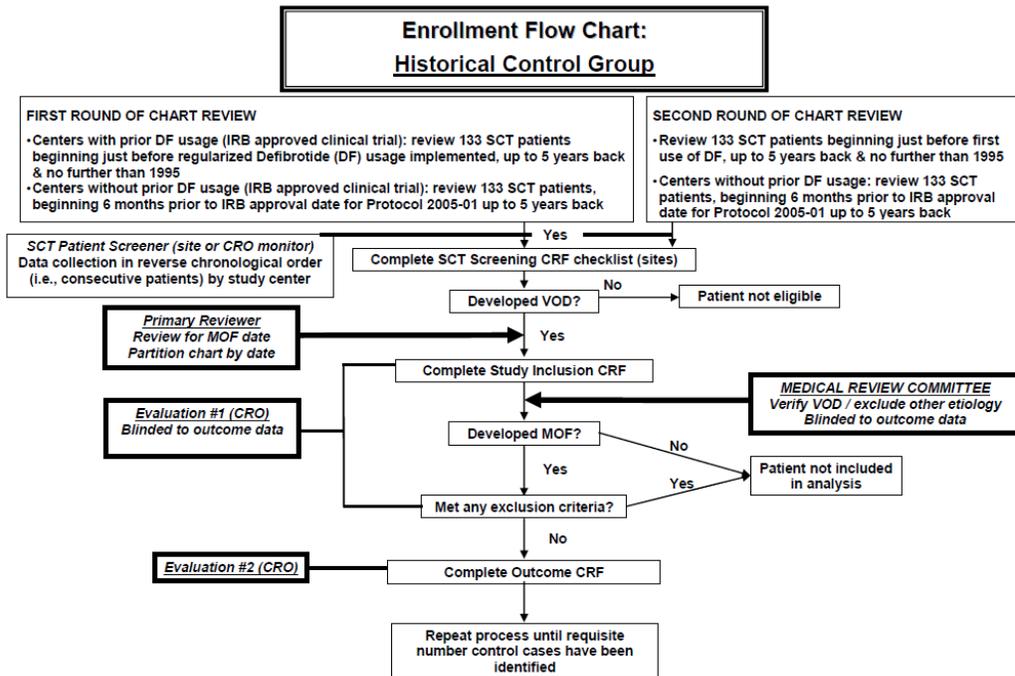
- 1- For sites that permitted contract research organization (CRO) personnel on-site to screen charts, CRO personnel did this at work
- 2- For those sites whose privacy laws mandated that only site personnel could review unredacted charts, site personnel did this work.

The algorithm outlining the criteria and timing of HC group selection by the MRC are provided in the following diagram.

Clinical Review  
 Tanya Wroblewski, M.D.  
 Donna Przepiorka, M.D. Ph.D.  
 NDA 208114  
 Defitelio (Defibrotide Sodium)

**Figure 1 Enrollment flow chart for the Historical Control Group**

(Source Study 2005-01 CSR, page 49/2943, Module 5.3.5.2)



The controls used to minimize bias in the selection of the final Historical Control Group are below:

- Multi-step Screening Process: At each center where HC patients were screened, charts of all bone marrow transplant recipients were sequentially reviewed by a screener in reverse chronological order. Cases were assessed to determine if there was evidence of VOD. For a patient with at least 1 observation of elevated total bilirubin, and at least 2 of the 3 additional VOD parameters present on the same day, these patients were further assessed for the presence of possible VOD associated pulmonary and/or renal dysfunction. If the case passed through this level or review conducted by the screener, then the chart was partitioned as of the date of possible eligibility and the case was sent to the MRC.
- Blinded Independent Medical Review Committee (MRC) - the final selection process was overseen by 2 expert hematologists at bone marrow transplant centers not involved in the conduct of the trial who were blinded to all outcome data.
- The MRC remained blinded to patient outcome by strict procedures to partition all

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

patient charts and case report from data. Outcome data, defined as any data beyond the date of VOD with MOF diagnosis, was not collected or entered on the case report forms until after the MRC made a positive decision regarding eligibility.

- Time Frame for Recruitment- Screening efforts for the historical control (HC) patients were performed starting 6 months prior to enrollment of patients into the defibrotide group at each individual site depending on when the site had routine access to defibrotide. Patient's selection for the HC group was limited to the time period from 6 months to the date of protocol activation of first defibrotide use with a stop date for all sites set at Jan 1, 1995.

### Dose Selection

The dose selected for Study 2005-01 of 6.25 mg/kg every 6 hours<sup>3</sup> was chosen based on efficacy safety results from a phase 2 dose finding study (study 99-118).

Study 99-118 was conducted comparing defibrotide doses of 25 mg/kg or 40 mg/kg/day for the treatment of VOD associated with organ dysfunction. There was no meaningful differences between the 25 mg/kg or 40 mg/kg/day dose with respect to complete response (CR) for the 25 and 40 mg/kg/day doses respectively or in survival at Day + 100 post-HSCT. The incidence of TEAEs was similar across treatment groups and there was a higher incidence (> 4%) of hemorrhage and hypotension reported in the 40 mg/kg/day group. Based on this dose ranging study, the 25 mg/kg/day dose was chosen indicating that this dose is more effective than lower dose (10 mg/kg/day) and effective as higher dose of 40 mg/kg/day but with improved safety profile.

### Study Treatments

Patients eligible for treatments were to receive their first dose of defibrotide the day they met study entry criteria or as soon as possible.

Patients were to receive 25 mg/kg/day of defibrotide given in 4 divided doses (approximately every 6 hours) at a maximum concentration of 4mg/ml with each dose to be infused over 2 hours.

### Dose Modification or Interruption

After at least 21 days of therapy, defibrotide may have been discontinued for patients who were discharged from the hospital. If VOD recurred, the patients would be readmitted and defibrotide therapy restarted at the same dose and infusion volume with which they were previously treated.

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

Defibrotide was to be discontinued for Grade 3 or 4 toxicities which were considered to be possibly, probably or definitely related to defibrotide by the Investigator. Defibrotide was also to be discontinued if significant bleeding occurred.

#### Prior and Concomitant Therapy

For the historical control and the defibrotide groups, medications were recorded from the date of transplant through discharge from the hospital + 30 days or Day + 100 post HSCT, whichever was sooner. In the historical control group, the use of tPA, heparin and other anticoagulation were not considered a protocol violation.

Medications used for chemotherapy or GVHD prophylaxis were recorded at study inclusion and additional details were collected after the study completed (determination of whether conditioning regimen was myeloablative or non-myeloablative, dosing information for medications as chemotherapy or GvHD Prophylaxis).

During treatment with defibrotide, it was recommended to keep platelets > 30,000/ul and hematocrit (HCT)> 30 with transfusion, INR < 1.5 and fibrinogen > 150 with factor replacement. Factor VII concentrates could have been used if deficiency expected or confirmed. Concomitant therapy with ATIII or low-molecular weight heparin was not allowed. The concomitant use of rapamycin for GvHD was not recommended and care regarding levels of FK506 (tacrolimus) were recommended.

Concomitant ursodial was allowed when it was already being used at the time of HSCT for prophylaxis. After defibrotide treatment was initiated, ursodiol was to be started only if gall bladder sludging was medical issue. Patients were not to be treated concurrently with medications that increased the risk of hemorrhage such as warfarin, non-steroidal anti-inflammatory drugs (NSAIDs), heparin, or systemic t-PA. Since preclinical data suggests that low-dose dopamine may divert splanchnic blood flow, it was recommended that this medication be terminated as soon as clinically possible.

#### Treatment Compliance

Defibrotide was administered by study center personnel. Temporarily delaying or stopping defibrotide was at the discretion of the Investigator. Details of administration of each divided dose of study medication, including delays or missed doses were recorded on the Case Report Forms (CRF).

#### Subject Completion or Withdrawal

Subjects could withdraw from the study at any time for any reason. The Investigator also could withdraw patients from the study if it was not in the best interest of the patient to continue. If

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

subject decided to withdraw, an End-Of-Treatment evaluation was performed.

### Adverse Events and Assessment of Safety

An adverse event is any undesirable sign, symptoms or medical condition occurring after starting the study drug through date of hospital discharge or Day + 100 post-SCT whichever is sooner even if the event is not considered related to the study drug.

Diagnostic and therapeutic non-invasive and invasive procedure will not be reported as adverse events. However, the medical condition for which the procedure was performed must be reported if it meets the definition of adverse event, unless it is a pre-existing condition.

Symptoms of the original or targeted disease are not to be considered adverse events in this study. The following symptoms are indicative of underlying disease (VOD with MOF) and will not be reported as adverse events (unless the event is considered serious): hyperbilirubinemia, elevated creatinine/renal failure, weight gain, encephalopathy, hypoxia/respiratory failure, ascites, hepatomegaly and right upper quadrant pain.

The following events are expected following stem cell transplant and will not be reported as adverse events (unless the event is considered serious): stomatitis, mucositis, infection febrile neutropenia, fatigue, loss of appetite, cytopenias, electrolyte disturbances, hypertension, abnormal lipid profiles, pneumonitis/pulmonary infiltrates, pericardial effusion and dyspnea.

Grading of Adverse Events: The National Cancer Institutes (NCI) Common Terminology Criteria for Adverse Events Version 3.0 will be used were applicable.

- 1- Each adverse event will be graded to describe intensity according the severity scale below. The NCI's CTCAE version 3.0 will be used were applicable. Mild: dose not interfere with patient's usual function
- 2- Moderate: Interferes to some extent with patient's usual function
- 3- Severe: Interferes significantly with patient's usually function
- 4- Life-threatening: puts the patient at immediate risk of death
- 5- Fatal: patient died

All adverse events will be followed until they are resolve or the patient's participation in the study ends (date of hospital discharge or Day + 100 post SCT whichever is sooner).

Patients in the treatment group will be asked at discharge to return to the study center at Day + 100 and Day + 180 post-HSCT for clinical laboratory studies and assessments for complete response and survival/mortality.

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

**Table 7 Schedule of Assessments for Study 2005-01**

(Source: Study 2005-01 Clinical Study Report page 36/2943, Module 5.3.5.1)

Schedule of Events	Study Entry	During Defibrotide Therapy		Cessation of Defibrotide <sup>3</sup>	Day+100 post-HSCT	Day+180 post-HSCT	Overall Survival
		Daily	Bi-weekly				
Informed Consent	X						X
Medical History	X						
Complete Physical Examination	X			X			
Vital Signs	X	X		X	X	X	
Weight	X	X		X	X	X	
Renal and Pulmonary Dysfunction Assessments <sup>1,9</sup>	X	X		X	X	X	
Clinical Assessments <sup>2,9</sup>	X	X		X	X	X	
Performance Status <sup>3</sup>	X	X		X	X	X	
Concomitant Medications	X	X		X	X		
Adverse Events	X	X		X	X		
Clinical Labs <sup>4,9</sup>	X	X		X			
Bilirubin <sup>5</sup>	X	X		X	X	X	
Fractionated excretion of sodium <sup>6</sup>	X			X			
Serum Creatinine	X	X		X	X	X	
Special Studies <sup>7</sup>	X		X	X			
Survival Status					X	X	X

<sup>1</sup> Per Section 6.2.2 of the final protocol in Appendix 16.1.1..

<sup>2</sup> Included assessment of ascites and hepatomegaly / RUQ pain.

<sup>3</sup> ECOG scale or Lansky scale for pediatric patients, as appropriate.

<sup>4</sup> CBC and platelets, PT, PTT, fibrinogen, BUN. Additional assessments determined to be clinically relevant including electrolytes (sodium, potassium, chloride, bicarbonate), liver function tests (AST, ALT, alkaline phosphatase, albumin, total protein) and WBC differential (including the absolute neutrophil count).

<sup>5</sup> Both total and direct.

<sup>6</sup> Defined as: (urine Na/urine Creatinine)/(serum Na/serum Creatinine)\*100. Were not to be measured if catheterization was required.

<sup>7</sup> 'Special studies' involved collecting blood for quantification of PAI-1 and other markers.

<sup>8</sup> Procedures occurring on "cessation of defibrotide therapy" may have occurred up to 72 hours following cessation of therapy, to accommodate patients whose defibrotide is stopped on a Friday or over the weekend.

<sup>9</sup> Additional assessments were collected whenever available through Day+180 per the reporting periods.

## Study Endpoints

### Primary endpoint

The primary endpoint is survival at Day + 100 post-HSCT. This was the original primary efficacy endpoint of the protocol.

*Reviewer Comment: VOD is generally a complication that occurs early in transplant (prior to day + 100 post HSCT, usually by Day + 28). Day + 100 HSCT is widely accepted as a standard endpoint for assessing patient survival following HSCT.*

### Secondary Endpoints:

The secondary endpoint is complete response by Day 100. Complete response was defined based on diagnostic criteria for severe VOD, and uses only objective clinical and laboratory parameters that can be assessed in both the historical control and defibrotide group.

The general parameters used to define CR are detailed below:

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

- Total bilirubin < 2mg/dL
- Resolution of associated organ dysfunction:
  - Renal:
    - Serum creatinine < 1.5 x baseline or meeting ULN based on patient's age
    - Creatinine Clearance/GFR ≥80% than initial value
    - Dialysis-independence
  - Pulmonary:
    - O2 saturation > 90% on room air
    - No supplemental O2 required
    - Ventilator independence

*Reviewer Comment: Due to the amount of missing raw data at the time of the initial NDA submission in 2011, the Agency requested additional raw data(laboratory values, information on pulmonary and renal status) to be collected and a derived CR analysis based on raw data and all data collected through Day + 100 was implemented.*

Additional secondary endpoints include survival rate at Day + 180 post SCT, overall survival and CR by Day + 180 post SCT and identification of potential serum and endothelial markers for VOD.

*Reviewer Comment: The analysis of survival or CR beyond Day+100 may not be as relevant in the determination of efficacy of defibrotide. Death beyond Day+ 100 is likely due to causes unrelated to VOD and more likely due to causes due to underlying disease or from other late occurring complications secondary to the transplant.*

### **Statistical Analysis Plan**

The primary analysis set is the Intent-to-Treat (ITT) population defined as all patients enrolled and treated in the defibrotide group and the patients in the final historical control group. The safety analysis set includes all patients with evidence of having received defibrotide in the defibrotide group and all patients in the final historical control group (Group A).

Screening and inclusion criteria are presented in listings by treatment group, historical control group and by site. The screening data for the historical control group includes all the screened patients who were diagnosed with severe VOD according to the MRC and the fraction of all screened patients who were enrolled in the final HC group.

### **Sample Size Considerations**

The original protocol specified that the sample size required at least 80 subjects in each group (Historical control and defibrotide). This would have provided 80% power and two-sided 0.05 significance level to detect a survival rate at Day + 100 post-HSCT of 0.4 in the defibrotide

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

cohort versus 0.2 in the historical control cohort.

*Reviewer Comment: The final sample size included 32 subjects in the Historical Control group and 102 subjects in the treatment group. After the MRC identified 32 patients out of approximately 7000 patients undergoing HSCT, the Applicant explored the feasibility of continued screening for additional historical control patients. Inclusion of new centers was not considered an acceptable option because enrollment to the defibrotide group had closed and continued screening at existing centers would have resulted in a less contemporaneous historical control group. The final sample size included 32 subjects in the Historical Control group and 102 subjects in the treatment group.*

#### Analysis Methods

The primary efficacy analysis and supportive and sensitivity efficacy analyses are based on propensity score methodology. Due to the non-randomized nature of the study and group membership, the calculation of the confidence intervals of the risk difference between treatment binary primary and secondary endpoint rates will be carried out using a propensity score. A propensity stratified and Koch weighted estimate of the difference in Day + 100 survival proportions is used with the two-sided 95% CIs and two sided p-value calculated using the Koch method.

For each patient in the ITT population, a propensity score/probability for belonging to the defibrotide group was calculated using logistic regression with the following baseline prognostic factors of survival as covariates:

- Ventilator and/or dialysis dependence(yes/no)
- ≤ 16 years of age(yes/no)
- Allogenic or autologous transplant(yes/no)
- Prior stem cell transplant(yes/no)

*Reviewer Comment: For further discussion regarding the analysis method specifically the propensity methodology see the statistical review by Yuan-Li Shen Ph.D. and Cindy Gao Ph.D..*

#### Interim Analysis

In the statistical analysis plan (SAP) there was 1 planned interim analysis, which specified to be performed when 40 patients in the defibrotide cohort with efficacy data available and approximately 80 controls with efficacy data available. This interim analysis was planned for either a sample size adjustment or a futility stop.

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

During the study, the Applicant performed 3 interim analyses in January 2008, May 2008 and September 2008 when there were 40(39%), 46(45%) and 61(60%) of patients in the defibrotide cohort with available efficacy data respectively.

*Reviewer Comment: The 2<sup>nd</sup> and 3<sup>rd</sup> interim analyses were unplanned however they occurred at the recommendation of the Data Safety Monitoring Board (DSMB). At the time of the initial planned interim analysis, DSMB could not make a decision regarding the stopping/increasing or continuing based on efficacy due to lack of sufficient data for proper analysis and the report of the DSMB was postponed until the May 2008 teleconference. The 2<sup>nd</sup> and 3<sup>rd</sup> interim analyses primarily discussed the criteria used to select the historical control and the practical application of those criteria in selection of the historical control to match the patients in the prospective study arm. The addition of the two interim analyses helped to assure the validity of the historical control arm and the overall validity and integrity of the trial.*

#### Protocol Amendments

**Table 8 Protocol Amendments For Study 2005-01**

<b>Date</b>	<b>Protocol Amendment</b>	<b>Key Elements of Protocol Amendment</b>
30 March 2006	Amendment 1	Screen start date for historical control patients set to begin 6 months prior to regular use of defibrotide in treatment arm. MRC added to verify patient selection, clarifications of definitions of severe VOD
4 December 2006	Amendment 2	Detailed procedures specified and maintenance of blinded data for eligibility screening. SAP modified regarding propensity scoring for stratification variables
14 June 2007	Amendment 3	FDA requested contemporaneous medical chart review for the creation of HC database, while also granting Emergency USE INDs made the ability to assemble a HC difficult. The original provision to allow chart review begin 6 months prior to treatment arm with defibrotide commence was allowed. And that medical chart review commence 6 months prior time frame. A second chart review with start date prior to the first use of defibrotide at each institution.
3 December 2007	Amendment 4	The primary efficacy endpoint was amended from survival at 100 days following stem cell transplant to comparison of the CR of severe VOD at Day + 100 post-HSCT between treatment groups. CR will incorporate only objectively defined parameters(bilirubin, renal function rests, resolution of need for supplemental oxygen, intubation or dialysis), survival at Day + 100 added as secondary endpoint
6 June 2013	Amendment 5	Study closed in April 2009, the FDA requested additional data from

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

Date	Protocol Amendment	Key Elements of Protocol Amendment
		<p>protocol in August 2011. The Sponsor did not reopen protocol and amendment 5 was to make several changes to include:</p> <ul style="list-style-type: none"> <li>• Change of primary endpoint from CR by Day + 100 to Survival at Day + 100 post-HSCT with CR by Day + 100 as secondary endpoint</li> <li>• Overall survival on all patients requested and included this data in CSR</li> <li>• Resolution of multi-organ failure required that all parameters of renal and pulmonary dysfunction resolved to defined a patient as having achieved a CR</li> <li>• Primary efficacy analysis amended to be performed on the ITT population</li> </ul>

*Reviewer Comment: During interactions with the Applicant and FDA, the Agency agreed in October 2007 that complete response (CR) in severe VOD may be a surrogate for mortality and may be used as the primary endpoint for Study 2005-01. The primary endpoint was changed to CR from severe VOD by Day + 100 post-HSCT. This change occurred midway through enrollment in the trial and thus not all data could be retrospectively captured for all patients (all elements of CR were not assessed on date of CR; elements of VOD were difficult to assess retrospectively in charts). After the August 2011 withdrawal of the NDA, the Applicant proposed to return to the original primary efficacy endpoint of survival at Day + 100 post-HSCT. In Feb 2013, the FDA agreed to this change.*

*The change in primary endpoint during the conduct of the trial resulted in missing data for complete response endpoint. Despite the changing of endpoints during the conduct of the trial, the validity of the primary endpoint of Day +100 survival is not called into question.*

**Data Quality and Integrity: Sponsor’s Assurance**

In response to the comments identified by the Agency in the August 2011 withdrawal letter, the Applicant implemented a data remediation plan, including additional data collection and source data verification activities. Full source verification of the study data was performed on all new data collected as well as any data that changed via query during the remediation process. In addition certain predefined critical variables for efficacy and safety were source data verified to ensure accuracy and completeness of data. Steps were also taken for standardization of laboratory values and audit reports are provided in the individual CRFs.

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

Data quality was addressed through the following:

- Quality check of the paper CRF's to the original SAS datasets
- Creation of a new 21CFR part 11 compliant database for the study that included additional fields requested by FDA
- Migration of SAS legacy datasets extracted from the initial submission into the new 21 CFR part 11 compliant database
- Edit checks for the study were re-tested and corrected where necessary
- Systemic review of the HC subjects and the Treatment Arm subjects through patient profiles add standardized listing were performed, leading to query generation and resolution
- Entry to the MRC adjudication data In the database
- Source document verification was performed at sites, where possible, to support the entry of all new data collected and any data that was changed via query outputs
- Remediation efforts occurred to collect missing lab names, normal ranges and accreditation. In cases, where lab ranges from the local lab are not available, generic range values were assigned.
- Updated statistical analysis plan to accommodate the presentation of new data
- Audit certificates are provided
- Overall survival data was added to the database for all but 5 patients from 2 sites  
Collection of additional OS data was attempted but not possible due to logistic and site challenges the Sponsor has documented these efforts.

*Reviewer Comment: The Applicant conducted a thorough data remediation plan and adequately addressed all the issues identified in the 2011 Complete Response letter.*

### 6.1.2. Study Results

#### **Compliance with Good Clinical Practices**

The Applicant provided attestation that the trial was conducted in accordance to the Declaration of Helsinki and US regulations covering the protection of human subjects, Institutional Review Boards and the obligations of clinical investigators in accordance with Good Clinical Practice(GCP).

#### **Financial Disclosure**

The Applicant has adequately disclosed financial interests/arrangements with clinical investigators. The financial disclosure information did not raise questions about the integrity of the data. See Appendix 13.2 of this review for details of the financial disclosure.

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

## Patient Disposition

### Patient Disposition for the Final Historical Control Group and the Defibrotide Group.

There were 102 patients enrolled in the defibrotide group and 32 patients enrolled in the historical control group. The reasons for cessation of defibrotide are not applicable to the historical control group and thus are not presented.

**Table 9 Final Disposition for the Historical Control and Defibrotide Group**

Patient Disposition	Defibrotide N=102 n(%)	Historical Control N=32 n(%)
ITT Analysis Set	102(100)	32(100)
Safety Analysis Set	102(100)	32(100)
<b>VOD Eligibility Requirements</b>		
Elevated total bilirubin	102(100)	32(100)
Hepatomegaly	84(82)	27(84)
Ascites	95(93)	27(84)
Weight Gain	98(96)	29(91)
<b>MOF by Day + 28 post-HSTCT</b>		
Yes	101(99)	32(100)
No	1(1)	0(0)
Average Day median(range)	13(1, 29)	N/A
<b>Defibrotide Cessation</b>		
Death	31(30)	Not Applicable(N/A)
Investigator Decision	22(22)	N/A
Patient Discharged	19(18)	N/A
Defibrotide Related toxicity	11(11)	N/A
Unrelated adverse events	9(9)	N/A
Consent withdrawn	3(3)	N/A
Other	7(7)	N/A
<b>Alive as of Day + 180</b>	33(32)	8(25)

MOF-multi-organ failure

The other reasons for defibrotide cessation in the defibrotide arm included “family decision to withdraw care, withdrawal of care, patient completed 21 day course, wife made decision for DNR, decreased renal function/fluids, biopsy showed no evidence of VOD, according to protocol, study medications was stopped on day 21 due to improved medical condition.”

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

### Timing and Selection of the Historical Control Group

Initially 6867 medical charts of patients undergoing HSCT were screened at 35 medical centers. The screening for the historical control occurred in two rounds. The start date for round one was set as 6 months prior to IRB approval at each center for a protocol using defibrotide in the treatment of severe VOD. Start date for round 2 was set as the date immediately prior to the first use of defibrotide at each participating medical center (either emergency-use or IRB-approved protocol). Different start dates were used due to the high number of emergency cases identified in round 1 of chart screening.

Seventeen sites participated in Round 1 and 18 sites participated in two rounds of screening. Reasons cited for participating in only one round of screening or a partial second round of screening include:

- 3 sites reached stopping date of Jan 1, 1995
- 8 sites had inadequate resources to perform a second round of screening
- 2 sites reached the date of its first HSCT patient
- 2 sites had been combined at the time for the HC screening period and split into adult and pediatric sites at the time of defibrotide enrollment.
- 2 sites were activated to the protocol towards the end of the defibrotide group enrollment period and insufficient time was available to screen cases.

The screeners reviewed 6867 charts and 6674 were deemed screen failures. This resulted in 193 charts with possible VOD identified. An additional 70 charts were excluded prior to the initial MRC review. A total of 123 patient charts were reviewed by the MRC over 9 months in a series of 12 conference calls (12 July 2007 and 19 February 2008). All 123 patients were re-reviewed one final time during July 2008 at a face-to-face meeting.

*Reviewer Comment: The 70 charts that were excluded prior to initial MRC review were not included as these were subjects who received defibrotide for emergency use. The selection of 32/6867 charts results in a selection of 0.5% of patients identified as meeting criteria for severe hepatic VOD with multi-organ failure. Taking into consideration that only qualified patients (severe VOD) received emergency use of defibrotide in the US during this time, the addition of the 70 patients to the 32 historical controls provides an overall incidence of severe VOD of 1.5%.*

Inclusion into the historical control arm spanned from 1995 to 2007 while recruitment into the defibrotide arm was between 2006 and 2008. The majority of patients for the final historical control group (21/32;66%) were recruited between years 2000-2006.

*Reviewer Comment: Although patients in the historical control arm were recruited from 1995 to 2007, the majority of patients were recruited between 2000 and 2006 which is more consistent*

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

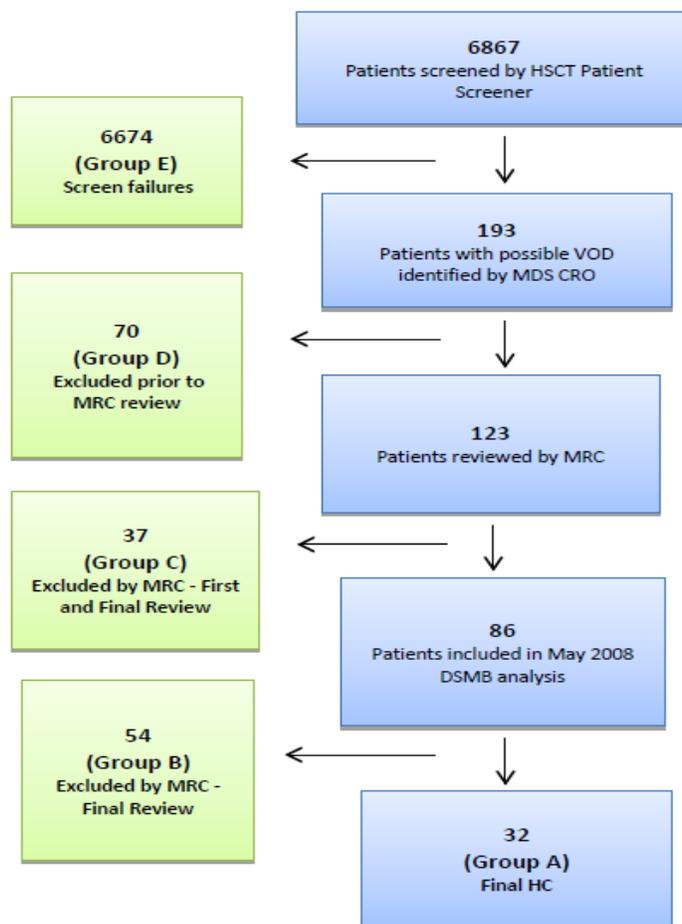
with the defibrotide arm. Despite improvement in supportive care for patients undergoing transplantation during the timespan, the mortality for patients with severe VOD with MOF has not improved (> 80%). Therefore, any potential temporal differences between the groups are not significant.

The reviewer acknowledges that the selection of the historical control group occurred concurrently with the defibrotide group. Due to the high mortality of hepatic VOD with end-organ failure there is no control group from prior randomized studies that are available to serve as a historical control. Given the limitations in external controls available, the selection of the historical control that occurred concurrently with defibrotide treatment group is acceptable.

The following figure and table better describe the selection process by the MRC.

**Figure 2 Selection of Historical Control Group**

(Source SAP v. 50, page 387, Module 5.3.5.1)



Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

The Historical Groups have been divided into Groups A-E based on available data. The following table profiles the description of the groups.

**Table 10 Description of the Historical Control Groups for Study 2005-01**

<b>Group(n)</b>	<b>Description</b>	<b>Data Available</b>
Group E (n=6674)	Subjects identified as having no signs of VOD by HSCT patient screener(screen failures)	Data to exclude patients provided in Inclusion/Exclusion and Screening CRFs
Group D (n=70)	Subjects identified as possibly having VOD by HSCT patient screener, but did not meet additional eligibility requirements and were excluded prior to MRC review	
Group C (n=37)	Excluded by MRC first and final review	Data to exclude patients provided in Inclusion/Exclusion and Screening CRFs  MRC Reason for exclusion provided in the MRS adjudication CRF
Group B Group B (n=54)	Excluded by MRC final review	
Group A (n=32)	Final Historical Control Group	Data to exclude patients provided in Inclusion/Exclusion and Screening CRFs  MRC Reason for exclusion provided in the MRS adjudication CRF  Safety and efficacy outcome data(VOD/MOF assessments, Day + 100 survival/Day + 180 survival, AEs, concomitant medications, laboratory values, vital signs, Physical exam listings, ECOG scores

MRC- Medical Research Committee

#### MRC Decision Making Process

The MRC initially assessed VOD parameters in regard to onset of toxicity in relation to HSCT and whether these were secondary to VOD or could be due to an alternate etiology. Over 100 patients were excluded due to VOD parameters that began prior to conditioning or HSCT. The possible alternative etiologies included the following:

## Clinical Review

Tanya Wroblewski, M.D.

Donna Przepiorka, M.D. Ph.D.

NDA 208114

Defitelio (Defibrotide Sodium)

- Hyperbilirubinemia: alternate etiology included GvHD, extravasation or drug induced hemolysis, preexisting cholestatic disease, prior hepatitis secondary to underlying immunodeficiency syndrome, bowel perforation and retroperitoneal bleed, gangrenous gallbladder, psychotropic medications, sickle cell disease and cholecystitis
- Ascites: alternate etiology included cholangitis, capillary leak syndrome and CHG
- Hepatomegaly: infiltration of liver with underlying disease, steatohepatitis, disseminated fungal infections, chronic liver disease secondary to ethanol injury
- Weight gain: Syndrome of inappropriate anti-diuretic hormone(SIADH), high dose cyclophosphamide preexisting cardiac myopathy, generalized edema and fluid overload

The MRC then assess pulmonary and renal dysfunction based for four parameters:

1. Onset of symptoms in relation to HSCT
2. Symptoms are secondary to VOD or ascribed to alternate etiology
3. Patient management resulted in amelioration of symptoms
4. Symptoms were sufficiently severe to warrant a diagnoses of VOD with associate d multi-organ failure

Possible alternate etiologies for pulmonary or renal symptoms included the following:

- Pulmonary: preexisting asthma, restrictive lung disease, pleural effusions with mechanical impingement from pre-existing hydronephrosis, pericardial effusion, capillary leak, CHG, fever induced oxygen de-saturation, fluid overload, TRALI, alveolar hemorrhage, infection and ARDS
- Renal: nephrotoxic drug

Lastly, the MRC excluded patients if the MRC did not feel confident in the diagnosis of VOD associated with multi-organ failure. The final review was conducted in July 2008 in a blinded fashion and the MRC did not have access to outcome information. Selection was made by consensus. The following table describes the reasons for the exclusion of the historical control groups B and C by the MRC.

**Table 11 Exclusion of Groups B and and C from Historical Control**

Exclusion	Historical Group And B N=86	
	Group B N=54	Group C N=37
<b>Primary Reason for MRC Exclusion</b>		
Alternate etiology for renal dysfunction	14(26)	3(8)

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

Exclusion	Historical Group And B N=86	
	Group B N=54	Group C N=37
Inadequate data for review	10(19)	0
Alternate etiology for severe pulmonary dysfunction	9(17)	5(14)
Alternate etiology for ascites, weight gain or jaundice	7(13)	16(43)
Alternate etiology for both pulmonary and renal dysfunction	7(13)	0(0)
Newly identified exclusion criteria	3(6)	0(0)
Lack of severe pulmonary dysfunction	2(4)	0(0)
Other Reasons	0(0)	12(32)

#### Exclusion of Group B (54 patients)

The MRC reviewed and screened the inclusion data for the 54 patients (Group B) who were declared as meeting protocol eligibility in the initial round of review. During the DSMB meeting in May 2008 the DSMB reviewed interim analysis results including 46 patients in the treatment arm and 86 patients in the control arm and recommended that the “ steering committee conform the criteria used to select historical controls and the practical application of those criteria”.

The Applicant sent a questionnaire to the 35 centers participating in the treatment group to better define the clinical aspects used for patients election. On finding was that investigators in the treatment group often waited 1-2 days following a possible diagnosis of VOD to alter management of a patient. Upon amendment to the MRC standard operating procedure, the MRC was allowed to query data from a potential historical control patient chart for a few days past the chart partition date via an independent physician with access to full chart.

*Reviewer Comment: Although the historical control was selected after the DSMB reviewing efficacy results, the selection of the historical control appears to have been conducted in rigorous process. The diagnosis of VOD is complex and is often in a continuum as competing causes are ruled out. The ability of the MRC to query charts for a few days past chart partition date is acceptable as this more accurately represents the investigator’s decision making process in the real time selection of patients. In addition, the additional chart query allows for more complete exclusion of alternate diagnosis.*

The final review was conducted July 2008 during the final DSMB analysis and reviewers were asked to use best judgment if patient had an unequivocal diagnosis of VOD with organ

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

dysfunction.

*Reviewer Comment: A review of the additional narratives for the ten patients that had inadequate charts for review was undertaken by this reviewer. An alternate etiology was provided in the narratives for each of these 10 patients and a definitive diagnosis of VOD could not be made.*

*Reviewer Comment: Although 54 out of 86 patients were excluded from the final historical control group due to alternate etiologies resulting in a small final historical control group (n=32), the historical control appears to be adequately and appropriately chosen. It is this reviewer's opinion that the final historical control group represents the best available control group given the complex and severe nature of the disease.*

### Protocol Violations/Deviations

Overall there were 11 critical protocol violations (22%) and 7(7%) major violations in the defibrotide group. A summary of major and critical protocol violations is provided in the table below.

**Table 12 Protocol Violations for Study 2005-01**

Protocol Violation, n(%)	Defibrotide N=102
<b>Critical</b>	22(22)
Concomitant Medication	8(8)
Inclusion/Exclusion	6(6)
Informed Consent Document	4(4)
Study Drug	1(1)
<b>Major</b>	7(7)
Study Drug	4(4)
Informed Consent Document	2(2)
Laboratory	1(1)
Visit Schedule	1(1)

Six patients in the defibrotide group entered with study without full compliance with the entry criteria. These 6 subjects are described in more detail below:

- Subject 08D02: The patient met Baltimore criteria of VOD by Day + 25, the VOD occurred on Day + 25 instead of the protocol-required Day + 21. The patient met pulmonary dysfunction criteria by Day + 28 and had renal dysfunction on study by Day + 37.
- Subject 08D03: The patient started defibrotide 3 days prior to renal MOF due to the

Clinical Review  
 Tanya Wroblewski, M.D.  
 Donna Przepiorka, M.D. Ph.D.  
 NDA 208114  
 Defitelio (Defibrotide Sodium)

sites incorrect calculation of creatinine clearance. The patient met pulmonary MOF on Day + 20.

- Subject 09D03: The patient met pulmonary dysfunction by Day + 23, however VOD occurred on Day + 28 rather than protocol required Day + 21.
- Subject 10D04: The Patient met Baltimore criteria of VOD by Day + 24, the VOD occurred On Day + 24 rather than protocol required Day +21.
- Subject 22D02: The patient met Baltimore criteria of VOD by Day 24 rather than protocol required Day + 21.

Five out of theses 6 subjects had symptoms of VOD by Day + 21 but diagnosis was not made until after Day 21.

*Reviewer Comment: The discrepancy with the timing of VOD diagnosis does not impact the overall study results.*

One subject (04D04), entered the Study with violation of the exclusion criteria. The subject is a 13 year old male with underlying diagnosis of T-Cell lymphoma was eligible for the protocol at the time of informed consent, but by the time of the first administration of defibrotide the patient no longer met hemodynamic stability. The patient was ventilator dependent upon trial entry and became dialysis dependent and developed septic shock and worsening hypotension and died five days after initiation of defibrotide.

### Table of Demographic Characteristics

Overall, the historical control group and the defibrotide groups were well matched with respect to gender, race, and age. The following table is a summary of patient demographics for the ITT Analyses Set for Study 2005-01.

**Table 13: Demographic characteristics of the primary efficacy analysis (ITT)**

Demographic Parameters	Defibrotide (N=102) n(%)	Historical Control (N=32) n(%)
<b>Sex</b>		
Male	64(63)	18(56)
Female	38(37)	14(44)

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

Demographic Parameters	Defibrotide (N=102) n(%)	Historical Control (N=32) n(%)
<b>Age</b>		
Mean years (SD)	26(21)	25(20)
Median (years)	21	18
Min, max (years)	(0,72)	(1,57)
<b>Age Group</b>		
≤ 16 years	44(43)	14(44)
> 16 - < 65 years	57(56)	18(56)
≥ 65 years	1(1)	0(0)
> 65 - < 75 years	1(1)	0(0)
≥ 75 years	0(0)	0(0)
<b>Race and Ethnicity</b>		
White	77(76)	23(72)
Latino/Latina	10(10)	1(3)
Black or African American	6(6)	2(6)
Asian	4(4)	2(6)
Native Hawaiian or Other Pacific Islander	1(1)	0(0)
Other	4(4)	4(13)

#### Summary of VOD Diagnosis

The following table provides a summary of the VOD diagnosis for the ITT Analysis Set. Within the defibrotide group, there were 4 patients who did not have a VOD diagnosis by Day +21 post-HSCT, which was a pre-specified inclusion criteria.

The median time to VOD diagnosis between the groups was similar with defibrotide (13 days) and historical control with 11 patients (75%) having a diagnosis of VOD by at least Day 17 or 14 in the HC and defibrotide groups, respectively. All patients in both groups met the eligibility criteria of bilirubin ≥ 2mg/dL.

**Table 14 Summary of VOD Diagnosis**

VOD Diagnosis	Defibrotide N=102	Historical Control N=32
<b>VOD Diagnosis by Day + 21 post HSCT</b>		
Yes	98(96)	32(100)
No	4(4)	0(0)

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

VOD Diagnosis	Defibrotide N=102	Historical Control N=32
<b>Time to VOD Diagnosis, days</b>		
Median, range	13(1,25)	11(4,19)
<b>VOD Diagnosis(bilirubin &gt; 2.0 mg/dl and ascites, weight gain)</b>		
All	91(89)	24(75)
Severe VOD due to renal	83(81)	21(66)
Severe VOD due to pulmonary	75(74)	21(72)

The wedged hepatic venous pressure gradient was only measured in 4 patients in the defibrotide treatment group and 1 patient in the historical control group.

#### Summary of Multi-Organ Failure Diagnosis

The historical control arm and the defibrotide treatment arm were well balanced with regard to MOF. There were more patients with renal dysfunction in the defibrotide group than the historical control arm. One patient did not have a diagnosis of severe VOD by Day + 28. The median time to severe VOD/MOF diagnosis was similar for both arms.

The following table describes the multi-organ failure diagnosis between the historical control group and the defibrotide group.

**Table 15 Multi-Organ Failure (MOF) Diagnosis**

MOF Diagnosis	Defibrotide n=102	Historical Control N=32
<b>Severe VOD diagnosis according to:</b>		
Pulmonary dysfunction	22(22)	8(25)
Renal Dysfunction	15(15)	1(3)
Both pulmonary and renal dysfunction	65(64)	23(72)
<b>Severe VOD diagnosis by Day + 28</b>		
Yes	101(99)	32(100)
No	1(1)	0(0)
<b>Times to severe VOD/MOF diagnosis (days)*</b>		
Median, range	13(1,29)	13(4,23)

\*Time measure from date of HSCT

*Reviewer Comment: Over 50% of patients had both renal and pulmonary dysfunction in both arms of the study. The high incidence of both renal and pulmonary dysfunction supports the proposed indication* (b) (4)

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

**Table 16 Central Nervous System (CNS) Function at time of VOD Diagnosis**

CNS Function at time of VOD Diagnosis, n(%)	Defibrotide N=102	Historical Control N=32
CNS Dysfunction due to other causes than VOD/MOF		
Yes	8(8)	9(28)
No	14(14)	7(22)
Not applicable	39(38)	9(28)
Missing	41(40)	7(22)

*Reviewer Comment: Due to amount of missing data and patients without CNS dysfunction, no definite conclusions can be drawn about the frequency of CNS dysfunction in patients with hepatic veno-occlusive disease with pulmonary or renal dysfunction that is due to the underlying VOD process.*

**Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)**

There are several other baseline demographic features that are unique to subjects undergoing a hematopoietic stem cell transplantation and include the following: baseline weight, underlying disease, disease status, and prior conditioning regimens, GVHD prophylaxis, and prior treatments. The following series of tables further describe these demographic findings between the defibrotide group and the historical control group.

**Table 17 Baseline Transplantation Demographics**

Demographic Parameters	Defibrotide Arm (N=102) n(%)	Historical Control (N=32) n(%)
<b>Baseline Weight(kg)</b>		
Median	60	58
Range	(4,135)	(6,111)
<b>Length of Hospitalization(days)</b>		
median	47	40
range	(6,191)	(13,148)
<b>GVHD prophylaxis at study entry</b>		
Sirolimus/tacrolimus	50(49)	5(16)
All other GVHD prophylaxis	49(39)	22(69)
No GVHD prophylaxis	12(12)	5(16)

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

Demographic Parameters	Defibrotide Arm (N=102) n(%)	Historical Control (N=32) n(%)
<b>Stratification factors</b>		
<b>Graft Type</b>		
Allogenic	90(88)	27(84)
Autologous	12(12)	5(16)
<b>Prior HSCT</b>		
Yes	13(13)	3(9)
No	89(87)	29(91)
<b>Age class</b>		
< 16 years of age	44(43)	14(44)
>16 years of age	58(57)	18(56)
<b>Ventilator/Dialysis-dependent at study entry</b>		
Yes	34(33)	7(22)
No	68(67)	25(78)

A notable difference includes a higher percentage of patients who were dialysis dependent at study entry. This difference was even more pronounced when looking at the pediatric populations (32% versus 0%) in the defibrotide vs historical control, respectively. Other differences include the use of GvHD medications at baseline with more patients in the defibrotide group (49%) using sirolimus/tacrolimus vs 16% in the historical control group.

*Reviewer Comment: The difference in dialysis dependence for both the pediatric population and overall population reflects a more serious disease at time of entry. There were approximately 10% more ventilator/dialysis dependent subjects enrolled in the treatment group compared to the historical control group. Despite this imbalance between groups, the treatment group had improved survival at HSCT Day 100 compared to the historical control group.*

Table 18 describes the underlying disease. The most common underlying diseases in both groups were acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), myelodysplastic syndrome (MDS) and neuroblastoma. Of note there were no patients in the historical control arm with neuroblastoma.

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

**Table 18 Summary of Underlying Disease**

Underlying Disease, n(%)	Defibrotide N=102	Historical Control N=32
Acute Myelogenous Leukemia	29(28)	8(25)
Acute Lymphoblastic Leukemia	17(17)	7(22)
Myelodysplastic Syndrome	7(7)	3(10)
Neuroblastoma	6(6)	0(0)
Non-Hodgkin Lymphoma	5(5)	2(6)
Chronic Myelogenous Leukemia(CML)	4(4)	1(3)
Myelofibrosis	4(4)	0(0)
Multiple Myeloma	3(3)	1(3)
HLH	3(3)	1(3)
Hurlers Syndrome	2(2)	0(0)
Osteopetrosis	2(2)	0(0)
Medulloblastoma	2(2)	1(3)
Juvenile Myelomonocytic Leukemia(JMML)	2(2)	0(0)

Other underlying diseases in the defibrotide treatment group with incidences of 1% or less included: Chronic Lymphocytic Leukemia (CLL), Waldenström's, Fanconi's Anemia, aplastic anemia, retinoblastoma, severe combined immunodeficiency, sickle-cell anemia, Tay-Sachs disease and thalassemia major.

The following table describes the disease status in the ITT Analysis Set. The majority of patients in the defibrotide group were in a first complete remission while the majority of patients in the historical control group were in a 2<sup>nd</sup> or later complete remission or untreated.

**Table 19 Disease Status ITT Analysis Set**

Disease Status	Defibrotide N=132	Historical Control N=32
1 <sup>st</sup> complete remission(stable disease)	29(28)	3(10)
2 <sup>nd</sup> or later Complete remission	14(14)	8(25)
Partial Remission	10(10)	1(3)
Relapse	14(14)	7(22)
Induction Failure	7(7)	1(3)
Untreated(MDS,AA)	19(19)	8(25)
Other	9(9)	4(13)

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

Summary of Prior Stem Cell transplantation.

The majority of patients had not received a prior transplantation (defibrotide 87.3%, HC 91%). Approximately 10% of patients in each group (defibrotide 11% and historical control 9%) had received one prior transplantations and 2 defibrotide patients had received two prior transplantations. The majority of patients underwent an allogenic transplant (88% and 84%) for the defibrotide and HC arms respectively. The following table describes the prior transplants, graft source and degree of match between the groups.

**Table 20 Summary of Transplant Type**

<b>Transplant Type N(%)</b>	<b>Defibrotide N=102</b>	<b>Historical Control N=32</b>
Autologous, n(%)	12(12)	5(16)
Allogenic, n(%)	90(88)	27(84)
Unrelated matched	29(32)	10(37)
Related matched	33(37)	11(41)
Unrelated mismatched	26(29)	5(19)
Related mismatched	2(2)	1(4)
<b>Source</b>		
Cord blood	24(27)	4(15)
Donor blood marrow	23(26)	13(48)
PBSC	41(46)	10(37)

The following table summarizes the conditioning regimen and GvHD prophylaxis for each treatment group.

**Table 21 Conditioning Regimens and GvHD Prophylaxis and Treatment for Study 2005-01 for the ITT Analyses Set**

<b>Conditioning Regimen n (%)</b>	<b>Defibrotide N=102</b>	<b>Historical Control N=32</b>
Cyclophosphamide	75(4)	26(83)
Buslfan	45(44)	14(44)
Fludarabine	23(24)	3(10)
Melphalan	21(21)	5(16)
ATG	20(20)	6(19)
Etoposide	15(15)	7(22)
<b>Number of days of conditioning therapy Median (range)</b>	6(2,13)	6(2,9)
<b>GVHD prophylaxis at study entry</b>	90(88)	27(84)
Sirolimus/tacrolimus	50(49)	5(16)
All others GvHD prophylaxis	40(39)	22(69)

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

Conditioning Regimen n (%)	Defibrotide N=102	Historical Control N=32
No GVHD prophylaxis	12(12)	5(16)
<b>GVHD Prophylaxis</b>		
Tacrolimus	50(49)	5(16)
Methotrexate	42(41)	20(63)
Cyclosporine	39(38)	23(71)
Mycophenolate mofetil (MMF)	29(28)	3(9)
Sirolimus	15(15)	0(0)
Methylprednisone/methylprednisolone sodium succinate	7(7)	10(31)
<b>Other therapeutic products</b>	41(40)	14(44)

The GVHD prophylaxis includes frequency  $\geq 3\%$ . Other agents that were used  $< 3\%$  include etanercept, ATG, immunosuppressant's, prednisone.

Additional conditioning regimens that were used less than 10% in both arms include carboplatin, thiotepa, alemtuzumab, carmustine, clofarabine, dexamethasone, gemtuzumab ozogamicin, mesna, rituximab, cytarabine.

*Reviewer Comment: A review of literature notes that the use of sirolimus in the GVHD prophylaxis regimen may improve transplantation outcomes, however this may be limited to non-VOD outcomes. A retrospective review of the use of sirolimus as GVHD prophylaxis may be associated with an increased risk of VOD after myeloablative transplantation (Cutler 2008). No definitive conclusions can be drawn regarding efficacy outcomes based on GHVD prophylaxis between the two treatment groups due to small numbers.*

#### Pediatric and Adult Enrollment in Study 2005-01

The following table provides a more detailed demographic breakdown of pediatric vs adult patients:  $\leq 16$  years versus  $> 16$  years of the ITT analysis set.

**Table 22 Adult versus Pediatric Patients in Study 2005-01**

Demographics	Defibrotide		Historical Control	
	$\leq 16$ years N=44	$>16$ years N=58	$\leq 16$ years N=14	$>16$ years N=18
<b>Gender, n(%)</b>				
Male	31(71)	33(60)	8(57)	10(56)
Female	13(30)	25(43)	6(43)	8(44)
<b>Age(years) at HSCT</b>				
Median	2.5	44.5	3.5	43.5
Range	(0,16)	(17,72)	(1,16)	(17,57)

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

Demographics	Defibrotide		Historical Control	
	≤ 16 years N=44	>16 years N=58	≤ 16 years N=14	>16 years N=18
<b>Length of Hospitalization</b>				
Median	49	43	43	36
Range	(11,191)	(6,121)	(13,148)	(14,148)
<b>GVHD prophylaxis at study entry</b>				
Sirolimus/tacrolimus	12(27)	38(66)	0(0)	5(28)
All other GVHD prophylaxis	25(52)	17(29)	13(93)	9(50)
No GVHD prophylaxis	9(21)	3(5)	1(7)	4(22)
<b>Stratification Factors</b>				
<b>Ventilator/dialysis dependent at study entry</b>				
Yes	14(32)	20(35)	0(0)	7(39)
No	30(68)	38(66)	14(100)	11(61)
<b>Graft type</b>				
Allogeneic	35(80)	55(95)	13(93)	14(78)
Autologous	9(21)	3(5)	1(7)	4(22)
<b>Prior HSCT</b>				
Yes	4(9)	9(16)	2(14)	1(6)
No	40(91)	49(85)	12(86)	17(94)

Demographic Comparisons between the Final Historical Control Group and the Excluded Historical Control Groups.

The following table provides the demographic comparison between the defibrotide group and the final historical control group A (32 patients) plus Group B (54 patients). Overall, the results were similar between the defibrotide group and the historical control groups of A+ B(86 patients). The baseline prognostic factors of survival at study entry were similar between groups. The major difference observed was in use of GvHD medications.

**Table 23 Comparison of Demographics between Historical Control Groups A and B versus Defibrotide**

Demographics	Defibrotide N=102	Historical Control Groups A + B N=86
<b>Gender</b>		
Male	64(63)	48(56)
Female	38(37)	38(44)

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

<b>Demographics</b>	<b>Defibrotide N=102</b>	<b>Historical Control Groups A + B N=86</b>
<b>Race and Ethnicity</b>		
White	77(76)	64(74)
Latino	10(10)	2(2)
African American	6(6)	4(5)
Asian	4(4)	3(4)
Other	4(4)	13(15)
<b>Age</b>		
Median, range	21(0,72)	18,(0,71)
Weight	60	57
Median, range	(4,135)	(4,111)
<b>Length of hospitalization</b>		
Median, range	47,(6,191)	37(7,229)
<b>GvHD prophylaxis at study entry</b>		
Sirolimus/tacrolimus	50(49)	18(21)
All other GVHD prophylaxis	40(39)	57(66)
None	12(12)	11(13)
<b>Stratification Factors</b>		
<b>Ventilator/Dialysis-Dependence</b>		
Yes	34(33)	18(21)
No	68(67)	68(79)
<b>Age class</b>		
≤ 16 years	44(43)	38(44)
>16 years	58(57)	48(55)
<b>Graft type</b>		
Allogeneic	90(88)	75(87)
Autologous	12(12)	11(13)
<b>Prior HSCT</b>		
Yes	13(13)	7(8)
No	89(87)	79(92)

Baseline prognostic factors were analyzed for differences between the defibrotide treatment group and Historical Control groups, A, B and C. With regard to Group B, a higher percentage of these patients had less severe study bilirubin (bilirubin < 5.0g/dl) at entry compared to Group A (78% versus 50%). Baseline parameters most related to prognostic factors of Day + 100 survival (ventilator/dialysis dependence, older age, acute leukemia, match/mismatch of the

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

donor/recipient) were well matched for Group B and the final Historical Control Group A.

**Table 24 Baseline Prognostic Factors between Defibrotide Group and Historical Control Groups A, B and C.**

Demographics	Treatment Group	Historical Control		
	Defibrotide N=102	Group A N=32	Group B N=54	Group C N=37
<b>Gender</b>				
Male	64(63)	18(56)	30(56)	24(65)
Female	38(37)	14(44)	24(44)	13(35)
<b>Race</b>				
White	77(76)	23(72)	41(76)	23(62)
Latino	10(10)	1(3)	1(2)	1(3)
African-American	6(6)	2(6)	2(4)	2(5)
Asian	4(4)	2(6)	1(2)	0
Other		4(13)	9(17)	11(30)
<b>Age</b>				
Median	21(0,72)	18(1,57)	20(0,71)	18(1,59)
<b>Weight kg</b>				
Median	60(4,135)	58(6,11)	57(4,108)	62(7,131)
<b>Stratification factors</b>				
<b>Ventilator/dialysis dependence</b>				
Yes	34(33)	7(22)	11(20)	13(38)
No	68(69)	25(78)	43(80)	23(62)
<b>Age Class</b>				
≤16 years of age	44(43)	14(44)	24(44)	6(43)
> 16 year of age	58(57)	18(56)	30(56)	19(51)
<b>Graft Type</b>				
Allogeneic	90(88)	27(84)	48(89)	32(87)
Autologous	12(12)	5(16)	6(11)	5(14)
<b>Additional Prognostic factors</b>				
Sirolimus/tacrolimus use, n(%)	50(49)	5(16)	12(24)	6(16)
Concomitant med that could increase hemorrhage, n(%)	10(10)	18(56)	15(28)	1(3)

**Treatment Compliance, Concomitant Medications, and Rescue Medication Use**

Defibrotide was infused intravenously under the supervision of health professionals, compliance is not an issue in this study.

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

### Concomitant Medications

All patients in either group (100%) received concomitant medications. The most common medications that could increase the risk of hemorrhage included heparin [defibrotide arm(5%) and Historical Control (44%)] and low molecular weight heparin (enoxaparin) [defibrotide arm (0%) and Historical Control (6%)].

The other common medications were ursodeoxycholic acid (defibrotide arm 70% and historical control 66%) and acetylcysteine (14%) in the defibrotide arm and 16% in the historical control arm.

Patients in both arms received at least one nephrotoxic medication defibrotide 99% and historical control 97%). Less patients in the defibrotide arm received nephrotoxic antibiotics (27% compared to 53% in the HC arm); patients in the treatment group more often received the liposomal formulation of amphotericin. The use of antimycotics such as caspofungin were used more frequently in the defibrotide arm compared to the HC arm (30% versus 16%).

*Reviewer Comment: There were no major differences between the defibrotide group and the Historical Control group with the use of agents such as ursodeoxycholic acid. The differences in nephrotoxic medication usage likely represents changing practice patterns and usage of newer less toxic formulations of antifungals. The difference in use of nephrotoxic medications is an improvement in supportive care but does not have impact on improvement in survival of hepatic VOD with multi-organ failure.*

### **Efficacy Results – Primary Endpoint**

The primary endpoint of Day + 100 survival post-HSCT in the defibrotide group was 38% (95% CI:29,48) versus 25%(95% CI:12,43) in the historical control group. The unadjusted difference in survival rate between these two cohorts was 13% with a p-value of (b) (4) from Chi-Square test (unadjusted).

**Table 25 Day + 100 post HSCT Survival Rate (Reviewer Table)**

<b>Survival Rate at Day + 100 post HSCT</b>	<b>Defibrotide N=102</b>	<b>Historical Control N=32</b>
Alive at day + 100 post HSCT, n(%)	39(38)	8(25)
95% Confidence Interval(exact method)	29,48	10,40
Observed Difference(95% CI)	13.2%(-4.6%, 31%)	
P-value from Chi-square test(unadjusted)	(b) (4)	

The primary analysis of survival (pre-specified in the SAP) was the survival difference calculated based on a propensity-score adjustment which provides for a means of adjusting prognostic

Clinical Review  
 Tanya Wroblewski, M.D.  
 Donna Przepiorka, M.D. Ph.D.  
 NDA 208114  
 Defitelio (Defibrotide Sodium)

factors in a non-randomized setting that may be unbalanced between groups.

The estimated difference in survival calculated by the Applicant using the propensity-stratified and weighted estimate is 23% with 95% CI (5%, 41%) with a p-value from Koch method of (b) (4). The FDA statistical review team was able to verify the estimated difference of 23% however the algorithms and ranking method used for the derivation of propensity score were not prespecified in the SAP. Therefore the statistical review team, depending upon strata and ranking order calculated the following estimated survival differences (see Table 26).

For full details regarding for discussion on the propensity score and additional analysis refer to the FDA statistical review by Yuan-Li Shen Ph.D. and Xin Gao Ph.D.

**Table 26 Analysis of Survival at Day + 100 using Propensity-Stratified and Weighted Estimate**  
 (Source: FDA Statistical Review)

Propensity Score Group	Survival at Day 100 Rate Difference	Nominal P-Value
<b>Sponsor's Primary Analysis</b>		
Quintile	23.0% (5.2%, 40.8%)	(b) (4)
<b>FDA Statistical Reviewer's Analyses</b>		
Quartile/Quintile Group	20.1% (2.1%, 38.2%)	(b) (4)
Equal space quintile	17.6% (-1.1%, 36.3%)	(b) (4)
Equal space quartile	16.1% (-1.6%, 33.8%)	(b) (4)
Unadjusted	13.2% (-4.6%, 31.0%)	(b) (4)

Note: To determine the propensity score cohort, "mean" algorithm was used for ranking method in the applicant's analyses and "high" algorithm was used for ranking method in the reviewer's analyses. This is realized by varying ranking options in PROC RANK in SAS. The confidence intervals and nominal p-values were adjusted by propensity score defined strata using the Koch method.

*Reviewer Comment: While the propensity score estimate was prespecified, the algorithms and ranking methods used in the adjusted analysis were not prespecified. The issue of the analysis plan not being sufficiently prespecified makes it difficult to interpret the magnitude of the treatment effect. The totality and consistency of an improvement in the mortality with the use of defibrotide provides enough weight of evidence to support the approval of defibrotide sodium for the treatment of patients with hepatic VOD (b) (4)*

*This reviewer acknowledges that unplanned adaptations were not prespecified in the SAP. The use of survival as an endpoint helps to overcome the bias that may be introduced due to the unplanned adaptations. While acknowledging the unplanned trial adaptations, it is the opinion of this reviewer that the consistent improvement in mortality demonstrated across all four of*

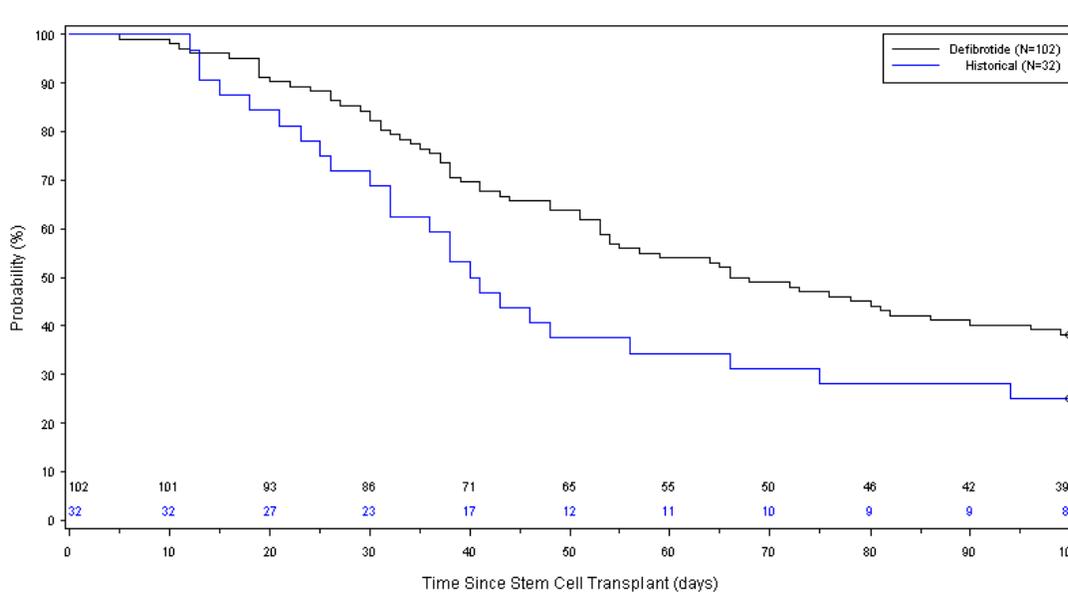
Clinical Review  
 Tanya Wroblewski, M.D.  
 Donna Przepiorka, M.D. Ph.D.  
 NDA 208114  
 Defitelio (Defibrotide Sodium)

*the studies with the use of defibrotide provides adequate evidence to support the approval of defibrotide in this rare and highly morbid disease setting.*

A time-to-event analysis of Day + 100 survival after transplantation was performed by the Applicant as supportive analyses. The following Kaplan-Meier estimate for survival at Day + 100 is presented in the figure below (taken from Applicants CSR page 120). This time-to-event analysis was verified by the FDA statistical review team.

**Figure 3 Time to Event Analysis of Survival at Day + 100 post-HSCT**

**Source: Applicants CSR Module 5.3.5.1 page 120.**



Number at risk shown in first line for defibrotide and in second line for Historical Control.

Defibrotide failed= 64(62%), Censored=39(38%) and Historical Control failed=24(75%) and censored=8(25%).

*Reviewer Comment: The time to event endpoint of survival at Day + 100 was not prespecified in SAP however the survival curve displays the survival data in a descriptive manner.*

**Sensitivity Analyses of the Addition of Historical Group B (54 patients)**

Additional sensitivity analyses were done to look at the addition of the 54 patients excluded in final MRC review to the Day + 100 survival. The following table describes the Day + 100 survival for both historical groups compared to the defibrotide arm.

Clinical Review  
 Tanya Wroblewski, M.D.  
 Donna Przepiorka, M.D. Ph.D.  
 NDA 208114  
 Defitelio (Defibrotide Sodium)

**Table 27 Day + 100 post-HSCT Survival Rate in Historical Groups (A + B)**

Survival at Day + 100	Defibrotide N=102	Historical Control N=86 (groups A Plus B)
Alive at Day + 100 post HSCT n (%)	39(38)	34(40)
95.1% Confidence interval (%)	29-48	29-49
Difference in rate*	4.4%	
95.1% Confidence Interval (%)*	-9.2-18.1	
p-value	(b) (4)	

\*based on Applicants Analyses of Survival Rate using the Propensity score and Koch method.

The following table shows the Cochran-Mantzel-Haenszel (CMH) test when comparing the defibrotide cohort versus the historical control cohort (86 patients). This table was calculated by the FDA statistical review team and includes Day + 100 survival for both groups.

**Table 28 Nominal P-values from CMH test when comparing Defibrotide cohort vs. historical control cohort B (86 patients)**

	Survival Rate at Day + 100
<i>Use Sponsor's developed propensity score</i>	
Quintile ('mean' algorithm)	(b) (4)
Quartile ('mean' algorithm)	(b) (4)
<i>Use Reviewer's developed propensity score</i>	
Quintile ('high' algorithm)	(b) (4)
Quartile ('high' algorithm)	(b) (4)
Quintile ('low' algorithm)	(b) (4)
Quartile ('low' algorithm)	(b) (4)

The addition of Historical Group B (N=54) to Group A (for a total of 86 historical controls) fails to demonstrate an improvement in Day + 100 survival post-HSCT.

*Reviewer's Comment: The treatment effect of defibrotide is not seen when the historical control group B is added to the primary historical control group A. The historical group B includes patients who did not have a definitive diagnosis of VOD and thus defibrotide would not have an effect on survival in this group.*

**Subgroup Analyses of Efficacy Study (Study 2005-01)**

The following table displays the Day + 100 survival outcomes for adult patients and pediatric patients in both the defibrotide group and historical control.

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

**Table 29 Summary of Subgroup Analyses of Efficacy**

	<u>Survival at Day + 100</u>	
	<u>Defibrotide</u>	<u>Historical Control</u>
<u>Age in years</u>		
<u>&gt;16(adult)</u>	<u>17/58(29%)</u>	<u>3/17(17%)</u>
<u>≤16(pediatric)</u>	<u>22/44(50%)</u>	<u>5/14(36%)</u>
<u>Transplant Characteristics</u>		
<u>Allogeneic</u>	<u>29/90(32)</u>	<u>7/27(26)</u>
<u>Autologous</u>	<u>10/12(83)</u>	<u>1/5(20)</u>
<u>Prior HSCT(yes or no)</u>		
<u>Yes</u>	<u>4/13(31)</u>	<u>0/3(0)</u>
<u>No</u>	<u>35/89(39)</u>	<u>8/29(28)</u>
<u>Ventilator/Dialysis Dependent at Study Entry</u>		
<u>Yes</u>	<u>8/34(24)</u>	<u>1/7(14)</u>
<u>No</u>	<u>31/68(46)</u>	<u>7/25(28)</u>

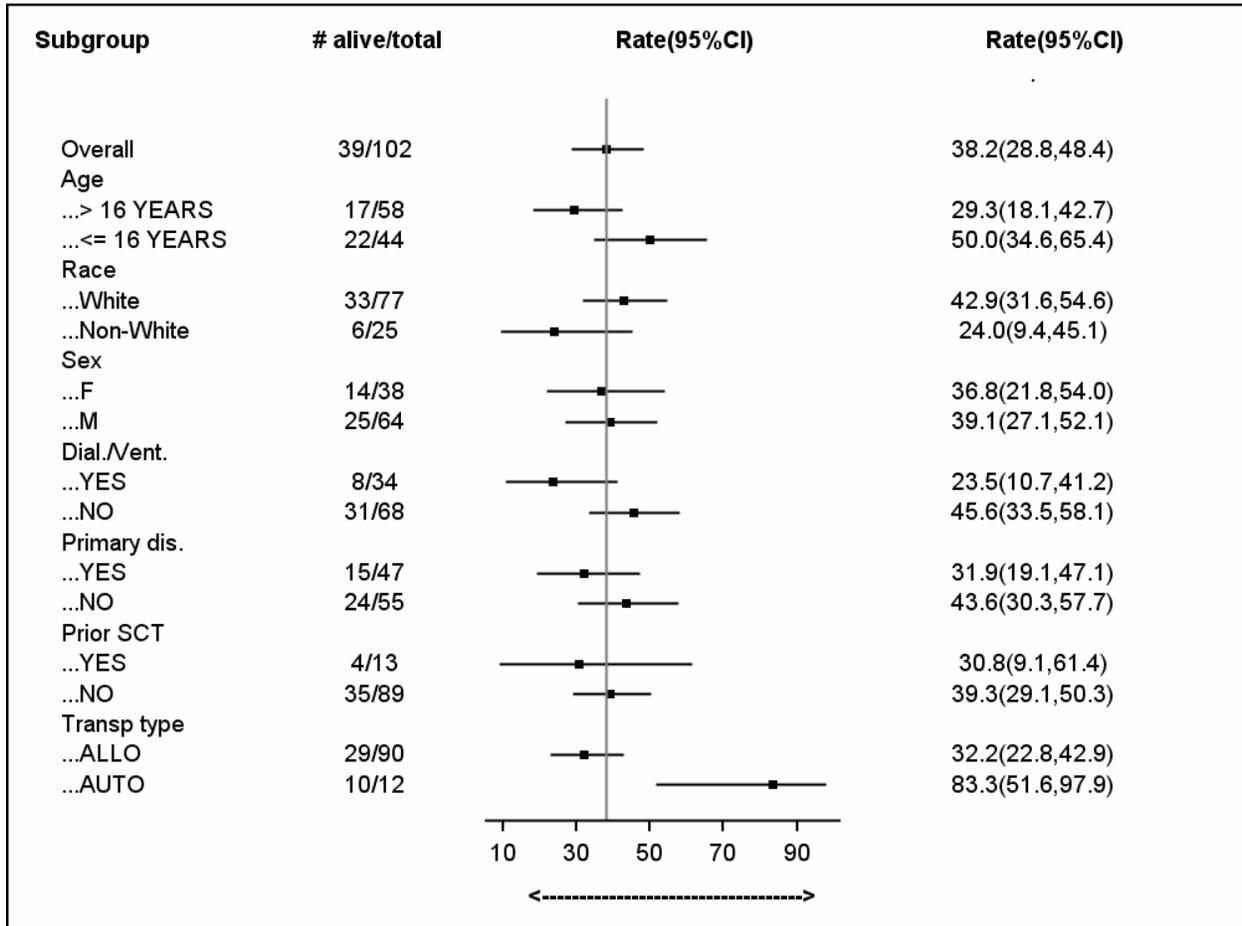
*Reviewer Comment: Improvement in survival outcomes were demonstrated in the defibrotide group compared to the historical control group across all baseline prognostic factors. The treatment effect of defibrotide is consistent between pediatric and adult patients.*

The following figure describes the efficacy outcomes of survival at day + 100 post HSCT for various subgroups in the defibrotide group. The FDA statistical review team devised the figure below.

Clinical Review  
 Tanya Wroblewski, M.D.  
 Donna Przepiorka, M.D. Ph.D.  
 NDA 208114  
 Defitelio (Defibrotide Sodium)

**Figure 4 Day + 100 post-HSCT Survival for Select Subgroups for the Treatment Group.**

Source: FDA Statistical Review Team



Day + 100 survival results with worse outcomes includes allogenic (32%) vs autologous (83%) transplant, prior transplant (yes: 31% versus no: 30%) and ventilator/dialysis dependence at study entry (yes: 24% versus no: 46%). Overall improvements in survival outcomes were seen in all subgroups in the defibrotide group even in patients with baseline prognostic factors associated with worse outcomes.

*Reviewer Comment: The differences and trends in survival between subgroups in the defibrotide arm are consistent with the known characteristics for the patient population. Due to the small numbers and lack of prespecification, subgroup analysis is exploratory.*

**Missing Data**

The main efficacy analyses was based on observed data, primary and secondary efficacy outcomes were observed for all patients in the ITT Analysis Set and no imputation was needed.

Clinical Review  
 Tanya Wroblewski, M.D.  
 Donna Przepiorka, M.D. Ph.D.  
 NDA 208114  
 Defitelio (Defibrotide Sodium)

### Data Quality and Integrity – Reviewers’ Assessment

There were several unplanned adaptations (sample size reduction and planned/unplanned interim analyses) and this poses a concern in determining the statistical significance level. The interim analyses that were implemented were done at the request of the DSMB to ensure appropriate data was available for assessment of safety and efficacy. In particular, the DSMB recommended that the historical control group enroll at least 80 patients, the Applicant and Agency agreed that continued screening for historical control patients would be unacceptable due to lack of contemporaneousness and addition of new centers. It was for these reasons that the sample size of 80 was not achieved in the Historical control group.

*Reviewer Comment: The planned or unplanned interim analyses occurred on the behest of the DSMB. The lack of ability to enroll 80 patients in the historical control group is acceptable based on reasons stated above. The rationale for the unplanned adaptations in the trial is acceptable.*

### Efficacy Results – Secondary and other relevant endpoints

The primary secondary efficacy endpoint for this study is complete response (CR) by Day + 100 post-HSCT for the ITT Analyses set. The rate of CR in the defibrotide group was 26% (95% CI: 17,34) versus 13%(95% CI: 1,24) in the historical control group. Table 30 further describes the secondary endpoint of CR.

**Table 30 Secondary Endpoint of Complete Response Rate**

Complete Response Rate by Day + 100 (ITT Analysis Set)	Defibrotide N=102 n(%)	Historical Control N=32 n(%)
CR by Day + 100 post-HSCT	26(26)	4(13)
95% Confidence Interval	17-34	1-24
Observed Differences, %(95.1% CI)	13%(-1%, 27%)	
Adjusted Difference *(95.1% CI)	19% (4%, 35%)	
p-value	(b) (4)	

\*Using propensity score defined strata and Koch method by statistical review team

For additional discussion regarding the estimated differences in the proportion using Koch method with propensity score models for the secondary endpoint, refer to the statistical review by Xin Gao Ph.D. and Yuan-Li Shen Ph.D.

*Reviewer Comment: The endpoint of CR while supportive of primary endpoint is lacking. Due to the amount of missing data and the required derived data to determine the CR rates, this endpoint should be considered supportive but cannot be fully substantiated.*

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

Additional secondary endpoints included Day + 180 survival post-HSCT and overall survival. The p-value for this analysis did not reach statistical significance and thus there was no difference seen for Day + 180 survival. There were 6 patients who died after Day + 100 in the post-HSCT group and all patients had a diagnosis of AML and cause of death included (malignant disease-2), infection (2 patients, chronic liver disease and GVHD. The following table describes the Day + 180 survival post-HSCT using the propensity weighted estimate.

**Table 31 Day + 180 Propensity Weighted Estimate using the Koch Method**

(Source: FDA Statistical Review Team)

	Summary statistics	Defibrotide. vs. Historical Control (N = 32)
<b>Applicant's analysis: Quintile</b>	Difference in rates 95% CI	4.4% (-9.1%, 18.0%)
	Nominal p-value	(b) (4)
<b>Reviewer's analysis: Quartile/Quintile Group</b>	Difference in rates 95% CI	3.9% (-9.6%, 17.4%)
	Nominal p-value	(b) (4)

*Reviewer's Comment: The survival advantage for defibrotide is seen only in the Day + 100 survival after transplantation. Survival at Day + 180 for this population is impacted by competing risks (disease relapsed, GVHD etc.).*

Overall Survival was an additional secondary endpoint. There was no difference in overall survival between the 2 groups. Table 32 describes the overall survival endpoint in Study 2005-01.

**Table 32 Overall Survival Rate**

Overall survival post-HSCT	Defibrotide N=102 N (%)	Historical Control N=32 N (%)
Overall survival post HSCT, n(%)	22(22)	7(22)
95% Confidence Interval	14-30	8-36
Median time(95% CI)	67(53,90)	41(30,60)

*Reviewer Comment: Similar to the Day + 180 survival results, overall survival in this population may be impacted by competing risks (disease relapsed, GVHD, transplant-related mortality).*

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

### **Dose/Dose Response**

Exposure-response analysis was not conducted for defibrotide because of insufficient PK data collected from patients participating in this trial. Patients were to receive 6.25 mg/kg every 6 hours given in 4 divided doses (every 6 hours) and treatment was to continue for a minimum of 21 days. Treatment was to be continued until the patient was discharged from the hospital.

**Table 33 Exposure for Study 2005-01**

<b>Exposure</b>	<b>Defibrotide N-102</b>
Days of Treatment	
Median	21.5(1,58)
Days of Treatment < 21 days	51(50)
Days of Treatment > 21 days	51(50)
<b>Duration of Treatment in days</b>	
Median, Range	22(1-60)
<b>Number of doses per day</b>	
Median, Range	3.90(0.8, 6.0)
<b>Daily dose mg/kg/day</b>	
Median, Range	24.4(5.0, 36.5)
Total number of doses received	
Median(range)	82(2,263)

### **Durability of Response**

The durability of response can be assessed by the Day + 100 survival.

### **Persistence of Effect**

Defibrotide is recommended to be administered for a minimum of 21 days and continued until hepatic VOD has resolved. Given the anticipated short-term usage of defibrotide loss of efficacy or tolerance effects are not anticipated. No additional analysis regarding persistence of effect was performed.

### **Additional Analyses Conducted on the Individual Trial**

No further analyses that were relevant to this trial were conducted by the clinical reviewer. Refer to the statistical review by Xin Gao Ph.D. and Yuan-Li Shen for further discussion and analyses regarding the propensity method calculations.

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

## 6.2. Study 99-118

### 6.2.1. Study Design

#### Overview and Objective

Study 99-118 entitled, “Defibrotide for Hematopoietic Stem Cell Transplant (SCT) Patients with Severe Hepatic Venous-Occlusive Disease (VOD): A Randomized Phase 2 Study to Determine the Effective Dose” was conducted at 9 medical centers in the US between April 2000 and May 2007. This study was an investigator-initiated study.

The primary objective of Study 99-118 is to determine the complete response (CR) rate of patients with severe VOD treated with defibrotide in the two treatment arms.

#### Trial Design

The study was a randomized, open-label, multi-center Phase 2 dose-finding study to determine the efficacy and safe dose of defibrotide in adult and pediatric patients with severe hepatic VOD post-hematopoietic stem cell transplantation.

Eligible patients were randomized to one of two defibrotide treatment arms in a 1:1 ratio. The randomization was stratified by prior cyclophosphamide conditioning and age (< 18 years, ≥18 years). Arm A was randomized to receive defibrotide 25 mg/kg/day and Arm B was randomized to receive defibrotide 40 mg/kg/day.

In both treatment arms, the starting dose of defibrotide on Day 1 was 2.5 mg/kg every 6 hours for 4 doses (total dose of 10 mg/kg/day) based on baseline weight (based on weight on date of admission to the bone marrow transplant unit) for conditioning. From Day 2, the defibrotide dose was increased to 6.25 mg/kg every 6 hours in Arm A (total dose of 25 mg/kg/day given in 4 divided doses) or 10 mg/kg every 6 hours in Arm B (total dose of 40 mg/kg/day) given in 4 divided doses.

Defibrotide was administered for a minimum of 14 days and treatment was to continue until the occurrence of CR. Defibrotide administration may be continued beyond 14 days if on Day 14 patient had evidence of response of any measure. Treatment was to be stopped if evidence of worsening of the clinical syndrome of VOD, unacceptable toxicity, or grade 3 or 4 adverse events considered probable or definitely related to VOD.

#### Key Inclusion Criteria

Patients with VOD defined by (Baltimore Criteria):

- Bilirubin ≥ 2mg/dL and 2 or more of the following

## Clinical Review

Tanya Wroblewski, M.D.

Donna Przepiorka, M.D. Ph.D.

NDA 208114

Defitelio (Defibrotide Sodium)

- Ascites
- Weight gain > 5% above baseline weight (defined as weight upon admission for BMT)
- Hepatomegaly or RUQ pain
- Patients with jaundice and reversal of flow on Doppler examination of the portal vein were eligible with 1 of the following: ascites, weight gain > 5% above baseline weight, hepatomegaly and RUQ pain.
- Patients with pre-existing hepatomegaly must have had documentation by physical examination or imaging that liver size was increased over baseline at admission.
- Patients with only 2 major criteria were eligible if they had biopsy proven VOD and characteristics of severe disease.
- Severity of VOD assessed by the Bearman (Bearman SI 1993) model and other methods. Patients addressed by the Bearman model (onset within 16 days of HSCT and conditioned with Busulfan/Cyclophosphamide (BU/CY), Cyclophosphamide/Total body irradiation (CY/TBI), or high dose cyclophosphamide/bis-chlorethynitrosourea (BCNU)/etoposide (VP-16) CY/BCNU/VP-16, were required to have a  $\geq 30\%$  risk of severe VOD.
- For patients not addressed by the Bearman model were required to have concomitant MOF defined as presence of 1 or more of the following: renal dysfunction (Creatinine  $\geq 2$  x value on date of admission to the BMT unit for conditioning or  $\geq 2$  x lowest value during conditioning, creatinine clearance or GFR  $\leq 50\%$  of admission value or dialysis dependence, pulmonary dysfunction (documentation of oxygenation saturation  $\leq 90\%$  on room air and requirement for positive pressure/ventilator dependence) not attributable to another cause and/or central nervous system dysfunction (documentation of confusion, lethargy, and/or delirium not attributable to another cause).
- Off heparin for at least 12 hours
- Eligible diagnosis of VOD within 35 days post-HSCT

### Key Exclusion Criteria

- Significant uncontrolled acute bleeding defined as hemorrhage requiring > 15cc/kg packed red blood cells to replace blood loss were excluded.
- Hemodynamic instability
  - No requirement for vasopressor support or being able to maintain mean arterial pressure within 1 standard deviation of age-adjusted levels with vasopressor support
  - Patients requiring renal dose dopamine alone (2 to 4ug/kg/min) were eligible without measurement of mean arterial pressure
- Grade B-D GvHD,
- Intubated for documented intrinsic lung disease
- Grade 4 neurotoxicity
- Currently receiving treatment with another experimental agent

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

**Concomitant Medications**

Concomitant treatment with ursodeoxycholic acid was not permitted. During the defibrotide treatment period it was recommended that hematology parameters be maintained at the following levels: platelets  $\geq 20 \times 10^9/L$ , HCT  $\geq 30\%$  (with transfusion as needed), PT  $\leq 15$  seconds and fibrinogen  $\geq 150$  mg/dL. Concomitant treatment with anti-thrombin III or low molecular weight heparin was not permitted.

**Table 34 Schedule of Assessments for Study 99-119**

Source: CSR page 27/1069, Module 5.3.5.2

<b>Assessment/procedure</b>	<b>Study Entry Period</b>	<b>Treatment Period</b>	<b>Follow-up Period</b>
Signed informed consent	X		
Review of inclusion and exclusion criteria	X		
Oncological, medical, and surgical history	X		
VOD <sup>a</sup> and MOF clinical assessment	X <sup>a</sup>	once daily	X
Bearman model for assessment of severe VOD risk <sup>b</sup>	X		
Physical examination	X	once daily	X <sup>c,d</sup>
Weight	X	once daily	X <sup>c,d</sup>
Vital signs	X	once daily	X <sup>c,d,g</sup>
ECOG Performance Status	X		
Room air oxygen saturation (or ventilatory settings)	X	once daily	X <sup>c,d</sup>

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

Assessment/procedure	Study Entry Period	Treatment Period	Follow-up Period
Dialysis (yes/no)	X	once daily	X <sup>c,d</sup>
Neurologic status assessment	X	once daily	X <sup>c,d</sup>
Clinical laboratory assessments			
Creatinine clearance	X		
GFR	X		
FeNa <sup>e</sup>	X		X <sup>c</sup>
Prothrombin time/partial thromboplastin time	X	once daily	X <sup>c</sup>
Complete blood count (including HGB and HCT)/platelet count	X	once daily	X <sup>c</sup>
Fibrinogen	X	once daily	X <sup>c</sup>
Bilirubin (total and direct)	X	once daily	X <sup>c,d</sup>
BUN/creatinine (urine)	X	once daily	X <sup>c,d</sup>
Special studies (including PAI-1)	X	twice weekly	X <sup>c</sup>
Pharmacokinetic sampling	X (Pre-dose Day 1)	Days 1, 2, 7	
Abdominal ultrasound with Doppler <sup>f</sup>	X		X <sup>c</sup>
Adverse events	X	X	X
Concomitant medications	X	X	X
Randomization		X	
Defibrotide dosing		X	
Vital status review (through Day +100 post-HSCT)		X	X

Note: The assessments included in this schedule are based on the study protocol and the case report form.

<sup>a</sup> The VOD clinical assessment included assessments of jaundice, ascites, weight gain, right upper quadrant pain, hepatomegaly and liver biopsy with WHVPG (if performed).

<sup>b</sup> Bearman model applied only to patients who had an onset of VOD within 16 days of HSCT and were conditioned with busulfan/cyclophosphamide, cyclophosphamide/total body irradiation, or cyclophosphamide/carmustine/etoposide.

<sup>c</sup> At Day 14 and again on the day defibrotide regimen was completed OR earlier if defibrotide is terminated prior to Day 14.

<sup>d</sup> Prior to discharge and as needed in the outpatient setting until CR is achieved.

<sup>e</sup> FeNa: Fractional excretion of sodium = (urine sodium/urine creatinine)/(serum sodium/serum creatinine)×100%. This assessment was to be omitted if catheterization was the only means to obtain the urine.

<sup>f</sup> Ultrasound investigation was to be documented with Doppler specifications as detailed in Appendix E of the clinical protocol in [Appendix 16.1.1](#). Ultrasounds may have been completed within 48 hours of time point specified in order to accommodate radiology scheduling.

<sup>g</sup> These data were collected but not entered into the clinical database as they were not needed to support analysis. Abbreviations: ECOG = Eastern Cooperative Oncology Group; FeNa = fractional excretion of sodium; GFR = glomerular filtration rate; HCT = hematocrit; HGB = hemoglobin; HSCT = hematopoietic stem cell transplant; MOF = multi organ failure; PAI = plasminogen activator inhibitor; VOD = veno-occlusive disease

## Study Endpoints

The primary efficacy variable was CR as defined as:

- Bilirubin < 2mg/dL after initiation of defibrotide (patients must have received a minimum of 3 days of defibrotide to be evaluable for response). For those patients who entered the study with severe VOD with MOF based on either renal, pulmonary or CCNS

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

dysfunction, resolution of the clinical syndrome was necessary to define the patient has having a CR.

The secondary endpoint was survival at Day + 100 post-HSCT.

#### Safety Measurements

Patients were to be followed for evidence of expected, potential AEs, for 30 days after the last dose, including bleeding, allergic reactions, vasomotor effects including flushing dizziness, headache and hypotension, nausea, vomiting, diarrhea, and fever. These AEs were to be reported only if life-threatening (Grade 4 or 5) as per the AE CRF page.

Safety Assessments included monitoring for AEs, physical examinations, clinical laboratory tests, and vital signs.

#### Statistical Analysis Plan

The as treated population comprised all randomized patients who received at least 1 dose of defibrotide. The evaluable population comprised all randomized patients who received a minimum of 3 consecutive days of defibrotide at the dose to which they were randomized and did not have any reason not be assessable for response.

The primary efficacy endpoint was CR rate. For this binary response variable, point estimates with 2-sided 95% confidence intervals (CIs) were reported for CR in the 2 treatment arms.

The secondary endpoint was survival at Day + 100 post-HSCT. For this binary outcome the proportion of patients who were alive at Day + 100 (point estimates with 95% CIs) together with a CI for the difference in proportions, assuming large sample normality was presented. Kaplan-Meier curves were presented to describe the distribution of time to death by Day + 100 and overall in each treatment arm. The log-rank test was used to compare the survival distributions between treatment arms.

The planned sample size estimate was based on the primary endpoint of the binary outcome of CR incidence (yes or no). At the time of final clinical protocol (22 October 2004) in which the final SS was estimated, the CR rate for the combined treatment arms was approximately 50%. Assuming a true response rate of 30% with 70 patients in each arm, the 95% CI for the CR rate was expected to be (18%-48%), sufficient to demonstrate a significant treatment benefit over the predicted CR for untreated patients based on historical data. The corresponding 95% CI was estimated to be (22-38%) for the 2 combined dose arms. It was anticipated that both doses would show activity in which case the dose with lesser toxicity would be taken forward.

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

#### Safety Analyses

Adverse events were coded from the verbatim term using the MedDRA version 16.0.

#### Protocol Amendments

**Table 35 Protocol Amendments for Study 99-118**

Date	Protocol Amendment	Key changes
8 Nov 1999	Original protocol	None
28 June 2000	Amendment 1	Dosing duration and discontinuation guidelines were changed to recommend that treatment be continued for a minimum of 14 days. Study schedule revised regarding assessments as both inpatient and outpatient until CR achieved
20 Nov 2000	Amendment 2	Eligibility criteria modified to exclude Grade 4 confusion and or delirium and patients who were receiving treatment with another experimental agent. Statistical Plan was modified to clarify the intent to enroll 30 evaluated patients
14 Sep 2001	Amendment 3	Exclusion criteria regarding concurrent GvHD was modified and an appendix added to address GvHD grading and to reflect transplant community of IBMTR Severity Index. Concomitant ursodial use was amended to state that ursodial could be used if the gallbladder was dilated and sludging sufficient to warrant surgical intervention or T-tube placement. Patient enrollment increased to 50 patients
2 Jan 2003	Amendment 4	Patient enrollment increased to 60 patients.
5 June 2003	Amendment 5	Secondary endpoints modified to include PK analysis and patient enrollment increased to 80 patients
18 Dec 2003	Amendment 6	PK sampling instructions in the appendices were modified
9 Feb 2004	Amendment 7	Enrollment increased to 100
1 Sept 2004	Amendment 8	Enrollment increased to 110
22 Oct 2004	Amendment 9	Enrollment increased to 140

#### Data Quality and Integrity: Sponsor's Assurance

Accurate and reliable data collected was assured by verification and cross-check of CRFs against the Investigator records by the study monitors(source document verification) and the maintenance of a drug-dispensing log by the investigational pharmacies.

The review process included targeted review of ambiguous TEAEs, including combined terms, non-specific raw terms related to infection or hemorrhage and non-specific terms that included "other". Any available verbatim text from individual patient CRFs that would allow more

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

specific coding of the AEs was appended to the raw data AE term and the data were then re-coded to the appropriate MedDRA code.

### 6.2.2. Study Results

#### **Compliance with Good Clinical Practices**

The Applicant provided attestation that this study was conducted in accordance with U.S. regulations governing the protection of human subjects, Institutional Review Boards, and the obligations of clinical investigators in accordance with good clinical practice (GCP).

#### **Financial Disclosure**

Study 99-118 was conducted under (b) (4) of which the Applicant has right of reference. Financial disclosure statements were not collected by the Investigator-Sponsor for investigators participating in this study as it was not considered a covered study under 21 CFR 54.2 at the time the trial was performed. The study was conducted in accordance with the policies of Dana-Farber Cancer Institute/Harvard Medical School (DFCR) which require mandatory adherence to strict de-minimis limits on the allowable financial interests of investigators participating in clinical research. There were no relevant disclosures, intellectual property or other resources paid to DFCR or the Investigator beyond research funding and honoraria with the de-minimis for his activities as part of an advisory committee. In addition, Study 99-118 was supported by two Orphan Drug Product grants, which in themselves required strict financial disclosure.

Financial disclosure statements were not collected for all investigators who participated in Study 99-118, it was expected that investigators were compliant with policies of their respective institutions. In addition, many of the investigators on study 99-118 later participated in the Gentium sponsored clinical study 2005-01 and or 2006-05. The Applicant provided a complete list of all investigators participating in Study 99-118 as well as a list of those investigators for whom the Sponsor has disclosure statements on file or certified on FDA form 3454.

*Reviewer Comment: The description of financial disclosure provided by the Applicant is acceptable and the financial disclosure information regarding study 99-118 that the Applicant was able to submit to the application during the review process do not raise questions about the integrity of the data.*

#### **Patient Disposition**

A total of 151 patients were randomized in this study at 9 medical centers between April 2000 and May 2007. Data for one patient could not be used in the final analysis as this patient began

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

emergency use of defibrotide therefore a total of 150 patients were considered to be randomized and enrolled in the study (75 in each treatment arm).

The primary reasons for discontinuation of defibrotide were similar between the two treatment arms. In both arms, the most common reason for discontinuation was resolution of VOD [25(33%) and 22(30%)] and VOD progression [11(15%) and 14(19%)] patients in the 25 mg/kg and 40 mg/kg groups, respectively. Treatment discontinuation due to death occurred in 10(13%) and 12(16%) of patients, respectively. Treatment withdrawal due to defibrotide-related toxicity was low in both groups [2(3%) and 4(5%)] respectively. Table 36 describes the patient disposition for Study 99-118.

**Table 36 Summary of Patient Disposition(All Patients) for Study 99-118**

<b>Variable</b>	<b>Defibrotide 25 mg/kg n(%)</b>	<b>Defibrotide 40 mg/kg n(%)</b>	<b>Total n (%)</b>
Patients enrolled	75	75	150
Patients Treated(with at least one dose)	75	74	149
<b>Reason for End of Defibrotide Treatment</b>			
VOD Resolved	25(33)	22(30)	47(32)
VOD Progression	11(15)	14(19)	25(17)
Death	10(13)	12(16)	22(15)
Defibrotide Toxicity	2(3)	4(5)	6(4)
<b>Other</b>	27(36)	22(30)	49(33)
AE, VOD Progression	2(3)	5(7)	7(5)
AE, VOD Resolving	2(3)	0(0)	2(1)
Alternative Diagnosis Superseded	4(5)	2(3)	6(4)
Patient Ready for Discharge(VOD Resolved)	9(12)	8(11)	17(11)
Withdrawal of Care	10(13)	7(10)	17(11)

### **Protocol Violations/Deviations**

There were 6 protocol deviations related to defibrotide dosing and included 4 patients who received less than 3 days of treatment, one patient received 5 doses rather than 4 doses in 24 hours and one patient who was randomized to the 25 mg/kg arm but when the exposure analysis was performed showed that the patient received doses closer to 40 mg/kg/day.

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

There were 2 inclusion criteria deviations to include one patient who was diagnosed with VOD based on bilirubin and ascites criteria with no documentation of hepatomegaly or RUQ pain on VOD diagnosis date and biopsy not performed. A second patient was diagnosed with viral hepatitis on liver biopsy with no evidence of VOD on liver biopsy.

There were 2 procedural deviations (weight not collected, physical exam not recorded) and there were 2 protocol violations of concomitant medications (two patients received heparin treatment). There were 2 protocol violations of concomitant medications to include administration of disallowed concomitant medication heparin in the 40 mg/kg treatment arm.

*Reviewer Comment: A listing of these protocol deviations was reviewed. Based on the nature of these protocol deviations, a significant impact on study outcomes would not be expected.*

### Demographic Characteristics

**Table 37 Table of Demographic Characteristics**

Variable	Defibrotide 25 mg/kg N=75	Defibrotide 40 mg/kg N=74	Total N=149
<b>Gender, n(%)</b>			
Male	41(55)	44(60)	85(57)
Female	34(45)	30(41)	64(43)
<b>Race</b>			
White	61(81)	57(77)	118(79)
Black	6(8)	7(10)	13(9)
Latino	4(5)	3(4)	7(5)
Asian	2(3)	4(5)	6(4)
Other	1(2)	3(4)	4(3)
<b>Age Category at HSCT</b>			
Median(years)	32	34	34
Range(years)	0.4, 61	0.6, 63	0.4, 63
≤ 16 years	22(29)	23(31)	45(30)
Infants and toddler (0-23 months)	5(7)	9(12)	14(9)
Children (2-11 years)	13(17)	10(14)	23(15)
Adolescents (12-16 years)	4(5)	4(5)	8(5)
>16 years	53(71)	51(69)	104(70)
<b>Weight kg</b>			
Median	66	66	66
Range	7-126	4-111	4-126

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

The demographic characteristics of the patient populations were similar for both arms of the study. The median age was 32 in the 25 mg/kg group and 34 in the 40 mg/kg group.

### Other Baseline Characteristics

The treatment arms were balanced with regard to the stratification variables [age ≥ 18 years: 52(69%) and 49(66%)] patients in the 25 mg/kg and 40 mg/kg treatment arms, respectively.

The most common underlying conditions were AML [18(24%) and 29(39%)], NHL[10(13%) and 9(12%) and ALL [11(15%) and 4(5%)] patients in the 25 mg/kg and 40 mg/kg treatment arms respectively.

The time to VOD diagnosis was similar in both arms with the median day to VOD diagnosis at 16 days and 15 days for the 25 mg/kg and 40 mg/kg arm, respectively. The most common VOD presentation was jaundice in both the 25 mg/kg arm and the 40 mg/kg arm.

In the 25 mg/kg defibrotide arm, the median days to determination of severe VOD was 17 days range (5, 35). There were generally 2-3 organs involved or compromised. The median oxygen saturation on room air was 92% for 62/75(83%) patients. There were 6 patients (8%) who were ventilator dependent at study entry. There were 3 subjects who were dialysis dependent at study entry and the median creatinine clearance at study entry was 1.6mg/dL for the 25 mg/kg arm.

**Table 38 Summary of VOD Diagnosis and Severity of VOD**

Variable	Defibrotide 25 mg/kg N=75	Defibrotide 40 mg/kg N=74	Total N=149
VOD Diagnosis Median Study Day <sup>a</sup> (Range)	16(4,35)	15(-1, 24)	16(-1, 35)
<b>VOD Indicators at Diagnosis, n (%)</b>			
Jaundice	70(93)	73(99)	143(96)
Ascites	53(71)	56(76)	109(73)
>5% weight Gain	60(80)	55(74)	115(77)
Hepatomegaly	56(74)	49(66)	105(71)
Right Upper Quadrant Pain	53(71)	47(64)	100(67)
<b>VOD Severity</b>			
<b>Pulmonary Dysfunction</b>			
Median Pulmonary Saturation on Room Air(range)	92 (78,99)	92 (80, 99)	92 (78,99)
Oxygen Saturation ≤ 90% on Room	20/62	24/54	44/116

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

Variable	Defibrotide 25 mg/kg N=75	Defibrotide 40 mg/kg N=74	Total N=149
Air at Study entry	(32)	(44)	(38)
Ventilator-dependent at Study entry	6(8)	5(5)	10(7)
<b>Renal dysfunction</b>			
Median Creatinine(mg/dL) at study entry(range)	1.6 (0.2, 5.0)	1.5 (0.2, 5.5)	1.5 (0.2, 5.5)
Dialysis-dependent at Study Entry, n(%)	3(4)	4(5)	7(5)

a-measured from date of HSCT

*Reviewer Comment: The Bearman model allowed for patients to enroll who have a risk of severe VOD > 30% based on the model. Therefore not all patients had evidence of multi-organ failure at the time of enrollment. Further analysis demonstrated that in the defibrotide(25 mg/kg) arm, 13(17%) patients enrolled based on diagnosis of VOD and a Bearman risk score of > 30%(range 30-60%). The majority of patients [62(83%)] met severity criteria with evidence of renal or pulmonary dysfunction.*

There was equal distribution between arms with regard to type of allograft and first or second transplant. The following table summarizes the conditioning agent, type of graft and GvHD prophylaxis.

**Table 39 Summary of Condition Agent, Graft Type and GVHD Prophylaxis**

	Defibrotide 25 mg/kg N=75 n(%)	Defibrotide 40 mg/kg N=74 n(%)	Total N=149 n(%)
<b>Type of graft</b>			
Allograft	67(89)	62(84)	129(87)
Autograft	8(11)	12(16)	20(13)
<b>Transplant number</b>			
1	68(91)	59(80)	127(85)
2	5(7)	13(18)	18(12)
Other	2(3)	2(3)	4(3)
<b>Conditioning Agent</b>			
Cyclophosphamide	61(81)	58(78)	119(80)
TBI	33(44)	35(47)	68(46)
Busulfan	32(43)	31(42)	63(42)
Melphalan	8(11)	15(20)	23(15)

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

	<b>Defibrotide 25 mg/kg N=75 n(%)</b>	<b>Defibrotide 40 mg/kg N=74 n(%)</b>	<b>Total N=149 n(%)</b>
VP-16	7(9)	5(7)	12(8)
BCNU	0	4(5)	4(3)
Other	27(63)	26(35)	53(36)
<b>GvHD Prophylaxis</b>			
Yes	67(89)	62(84)	129(87)
Not applicable	6(8)	9(12)	15(10)
<b>Type of GVHD Prophylaxis</b>			
Methotrexate	43(57)	35(47)	78(52)
Cyclosporine	38(51)	35(47)	73(49)
Other*	45(60)	39(53)	84(56)

\*Other- not specified in clinical study report or datasets

### Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The study drug is infused intravenously under the supervision of health professionals, compliance is not considered an issue in this study.

### Efficacy Results - Primary Endpoint

The results of the primary efficacy variable of CR in the as treated population revealed that 35 patients (47%) in Arm A and 30 patients (41%) in Arm B were considered to have a CR. The difference between the groups was not statistically significant with a p-value of (b) (4). The following table provides the overall summary of CR for Study 99-118.

**Table 40 Complete Response Rate for Study 99-118(Reviewer's table)**

	<b>Defibrotide 25 mg/kg N=75</b>	<b>Defibrotide N=74</b>
Complete Response Rate	25(47%)	30(41)
95% CI	35-58	29-53
Difference in rate(%)	6.1	
p-value	(b) (4)	

\*95% CIs on point estimates using exact methods. P-value from Cochran Mantel Haenszel test.

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

Comparison of time to CR did not demonstrate any difference between the two dose groups. The median time to CR for those patients who achieved a CR was 41 days and 44 days respectively from Arms A and Arm B.

*Reviewer Comment: The complete response rates in study 99-118 for both arms (25 mg/kg and 40 mg/kg) were higher than response rates seen in Study 2005-01. This difference may be explained by the different definitions for CR in the two trials.*

#### **Data Quality and Integrity - Reviewers' Assessment**

No trial design or conduct issues that might influence the efficacy results were discovered.

#### **Efficacy Results - Secondary and other relevant endpoints**

Survival at Day + 100 after transplantation was a key secondary efficacy endpoint in this study. The analysis was between the 25 mg/kg/day treatment arm and the 40 mg/kg/day treatment arm. In this analysis, patients without reported death by Day + 100 were considered alive and were censored at the patient's last known date alive or the last scheduled time point in the follow-up interval.

**Table 41 Day + 100 post HSCT survival (Reviewer's table)**

<b>Variable</b>	<b>Defibrotide 25 mg/kg N=75</b>	<b>Defibrotide 40 mg/kg N=74</b>	<b>Total N=149</b>
Survival by Day + 100, n(%)			
Alive 95% CI	33(44) [33,55]	28(38) [27,49]	61(41) [33,49]

*Reviewer Comment: Although the survival is similar between the two arms, there were more treatment-emergent adverse events in the higher defibrotide dose arm and thus the lower dose arm was the dose selected for further study in the pivotal trial. The Day + 100 survival in the 25 mg/kg group is similar to the Day + 100 survival post-HSCT treatment effect seen in the pivotal study 2005-01. See the statistical review by Cindy Gao Ph.D. and Yuan-Li Shen Ph.D. for additional statistical details.*

Key exploratory analysis for subgroups for the secondary endpoint of survival at Day + 100 post HSCT for the indication population (defibrotide group 25 mg/kg) demonstrated that survival rates were higher for pediatric patients receiving 25 mg/kg compared to adults (68% vs 39% for patients  $\geq 16$  years and  $> 16$  years of age, respectively).

*Reviewer Comment: There is a treatment effect across the adult and pediatric populations.*

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

### Dose/Dose Response

Responses were observed across both dose levels for this phase 2 study and there are no meaningful differences between the 25 mg/kg/day or 40 mg/kg/day groups or in survival (or CR). There was a higher incidence (> 4%) of treatment related TEAEs, SAEs, fatal TEAEs and TEAS of hemorrhage and hypotension in the 40 mg/kg /day dose group. Therefore the 25 mg/kg /day was chosen based on efficacy and safety.

**Table 42 Defibrotide Exposure for Study 99-118**

	<b>Defibrotide 25 mg/kg N=74</b>	<b>Defibrotide 40 mg/kg N=75</b>	<b>Total N=149</b>
<b>Number of doses</b>			
Median (range)	75 (6,325)	71 (5,239)	74 (5,325)
<b>Length of treatment</b>			
Median (Range)	20 (3,93)	21 (2,70)	20 (2,93)
<b>Number of Days of Treatment</b>			
Median (Range)	20 (3,83)	20 (2,62)	20 (2,83)
<b>Average Daily Dose Received(mg/kg/day)</b>			
Median (Range)	22.4 (8-26)	34 (10-41)	24 (8-41)

### Durability of Response

The durability of response can be assessed by the complete response rate (primary endpoint) and secondary endpoint of survival.

### Persistence of Effect

Defibrotide is recommended to be administered for a minimum of 21 days and continued until hepatic VOD has resolved. Given the anticipated short-term usage of defibrotide loss of efficacy or tolerance effects are not anticipated. No additional analysis regarding the persistence of effect was performed.

### Additional Analyses Conducted on the Individual Trial

There were no additional analyses of Study 99-118 relevant to this review.

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

### 6.3. CIBMTR Database Study

#### 6.3.1. Study Design

##### Overview and Objective

The CIBMTR study is entitled, “Defibrotide for the Treatment of Hematopoietic Stem Cell Transplant (HSCT) Patients with Severe Hepatic Venous-occlusive Disease (VOD): Data from the Center for International Blood and Marrow Transplant Research (CIBMTR) Database.

This study was designed to provide additional supportive efficacy data independent of Study 2005-01 for the treatment of severe hepatic VOD in HSCT therapy. The timeframe for this analysis was limited to patients transplanted between November 1, 2008 and December 31, 2011 whose data was reported to the CIBMTR on the Comprehensive Report Form (CRF). This time frame was selected to ensure that there was no overlap between the CIBMTR registry patients and subjects who participated in Study 2005-01 (last patient enrolled in June 2008 with primary Day + 100 post-HSCT follow-up completed by October 2008).

The objectives of this study are as follows:

- To obtain data from the CIBMTR registry database to provide the basis for evaluation of defibrotide in the treatment of severe hepatic VOD in HSCT patients by defining a defibrotide-treated and non-defibrotide-treated populations
- To evaluate defibrotide treatment in these populations for the following efficacy endpoints:
  - Survival (dead/alive) Day + 100 post-HSCT
  - Time to death by Day + 100 post-HSCT
  - VOD Resolution by Day + 100 post-HSCT
  - Survival (dead/alive) to Day + 100 after the onset of VOD
  - Time to death by Day + 100 after the onset of VOD
- To evaluate selected parameters of transplant-related morbidity in these populations, specifically failed or delayed engraftment and acute graft-versus host disease (aGVHD)
- To evaluate the primary cause of death at Day + 100 post-HSCT

##### Trial Design

CIBMTR collects data at 2 levels: Transplant Essential Data (TED) and Comprehensive Report Form (CRF) data. Datasets for analysis were compiled by extracting data from the CIBMTR’s Research Data Database. Defibrotide-treated and non-defibrotide treated patients who were diagnosed with severe hepatic VOD in a setting of renal and/or pulmonary dysfunction were identified for evaluation using the criteria below:

## Clinical Review

Tanya Wroblewski, M.D.

Donna Przepiorka, M.D. Ph.D.

NDA 208114

Defitelio (Defibrotide Sodium)

- CIBMTR Form 2400, Revision 2: Pre-transplant Essential Data
- CIBMTR Form 2000, Revision 2: Recipient Baseline Data
- CIBMTR Form 2006, version 1.0 and Version 2.0: Hematopoietic Stem Cell Transplant Infusion
- CIBMTR Form 2100, Revision 2: 100 Days post-HSCT Data
- If needed- CIBMTR Form 2200, Revision 2: 6 months to 2 years post-HSCT Data (for Day + 100 survival data only if data unavailable from 2100)
- CIBMTR Form 2900, version 1.0 Recipient Death data

There were no formal prespecified sample size calculations undertaken for this investigation as there was no planned sample size. The final patient population for analyses included 96 patients with severe VOD. Fifty-five patients did not receive defibrotide and 41 received defibrotide for treatment of VOD.

Selection criteria were prospectively defined to identify a group of HSCT recipients within the CIBMTR database who met the diagnosis of severe hepatic VOD (in setting of severe hepatic or renal dysfunction). The diagnosis of VOD was made according to the guidance provided in the CIBMTR Manual for the CRF (Form 2100) and included the following for the fulfillment of criteria for VOD (McDonald et. al. 1984 and Jones et. al. 1987):

- Jaundice (bilirubin > 2mg/dl)
- Hepatomegaly with RUQ pain
- Ascites and/or weight gain

For a patient in the CIBMTR register to have been considered as having severe VOD criteria for VOD diagnosis must have been met along with either criterion for organ impairment: renal and/or organ impairment pulmonary.

### **Study Endpoints**

The primary efficacy endpoint was a binary outcome: survival (dead/alive) at Day + 100 post-HSCT with Day 0 being the date of HSCT.

The secondary endpoints included:

- Time to death measured from
  - Time of HSCT to last date of contact at the time of data cutoff
  - The date of VOD diagnosis to last date of contact at the time of data cutoff
  - VOD resolution

The safety endpoints were evaluated to assess transplant-related mortality and included neutrophil and platelet engraftment, secondary graft failure, acute GvHD, and the primary cause of death at Day + 100 post-HSCT.

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

### **Statistical Analysis Plan**

All analyses were performed by CIBMTR personnel. All patients who satisfied the selection criteria and had an HSCT date between November 1, 2008 and December 31, 2011 were included in the study. With 55 patients and 41 patients in the non-defibrotide and defibrotide treated arms, respectively, the standard error for a treatment difference of 10% in terms of Day + 100 death rates is less than 0.103 and the width of the 95% CI is less than +/- 0.202

The method of analyses for all endpoints focuses on summary statistics and exploratory evaluation rather than formal inference in terms of p-values. Confidence intervals were calculated to provide estimates of potential treatment benefit.

### **Protocol Amendments**

There were no changes in the conduct of the study or planned analyses.

### **Data Quality and Integrity: Sponsor's Assurance**

Participating transplant centers were required to report all transplant consecutively and compliance was monitored by on-site audits conducted by CIBMTR. The CIBMTR on-site data audit program includes the following steps and processes: audit cycles (4 years), recipient selection and eligibility requirements, forms and data fields and methodology.

## **6.3.2. Study Results**

### **Compliance with Good Clinical Practices**

The study report for the CIBMTR data registry review includes a statement that the study was performed in compliance with all applicable federal regulations pertaining to the protection of human research participants. Protected Health Information used in this study was collected and maintained in CIBMTR's capacity as a Public Health Authority under the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule.

### **Financial Disclosure**

The Applicant has adequately disclosed financial interests/arrangements with clinical investigators. This was a retrospective chart review. There were no questions about the integrity of the data.

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

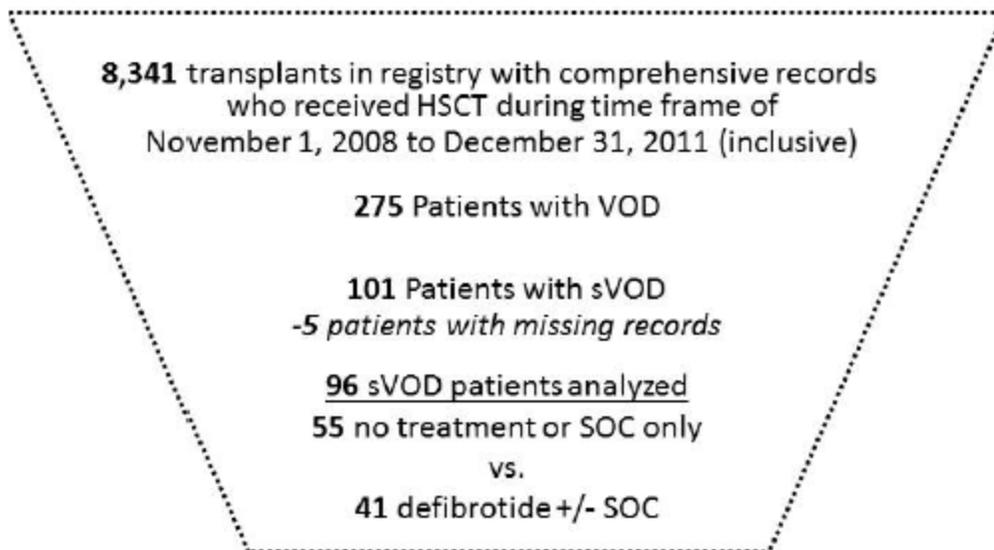
### Patient Disposition

At the time this database was prepared (final dataset November 5, 2013), the CIBMTR research database included 8341 patients transplanted between November 1, 2008 and December 31, 2011 for whom CRF data was available. Within this patient population a total of 275 patients were reported with VOD. Of these patients, 101 were identified as having severe VOD.

Of these 101 patients, 5 were excluded due to missing VOD treatment data. Therefore the final patient population includes 96 patients with severe VOD. The following figure depicts the flow of patient selection.

### Figure 5 CIBMTR Patient Selection

(Source: Clinical Study Report Page 28, Module 5.3.5.2. )



*Reviewer Comment: The CIBMTR registry data included 8341 patients of which 275 were reported to have VOD with only 96 patients meeting the eligibility for severe VOD with an incidence of 1.2% (96/8341) which is similar to incidence of severe VOD identified in the historical control group (1.5%).*

### Protocol Violations/Deviations

Protocol violations/deviations are not applicable since this was a retrospective review of CIBMTR database.

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

Demographic Characteristics

**Table 43 Table of Demographic Characteristics**

Demographic Parameters	Defibrotide (N=41) n(%)	Non-Defibrotide (N=55) n(%)
<b>Gender</b>		
Male	19(46)	40(73)
Female	22(54)	15(27)
<b>Age</b>		
Median (years)	11	31
Min, max (years)	(<1,64)	(<1,67)
<b>Age Group</b>		
≤ 16 years	25(61)	11(20)
≥ 17 - < 65 years	16(39)	42(76)
≥ 65 years	0(0)	2(<1)
> 65 - < 75 years	0(0)	2(<1)
≥ 75 years	0(0)	0(0)
<b>Race and Ethnicity</b>		
White	33(81)	45(82)
Latino/Latina	11(27)	9(16)
Black or African American	3(7)	4(7)
Asian	3(7)	3(6)
Native Hawaiian or Other Pacific Islander	0(0)	1(2)
Other	2(5)	1(2)

*Reviewer Comment: In the defibrotide group 61% of patients were less than age of 16 compared to 20% in the non-defibrotide group. Reports in the literature have described that pediatric patients have a survival advantage compared to adults after a diagnosis of severe VOD who receive defibrotide. Other factors to include in survival outcome include age at transplant and underlying disease (non-malignant versus malignant) may drive the improvement in survival. In general, pediatric patients generally have better survival outcomes compared to adults post-transplantation. No definitive conclusion can be drawn regarding superior benefit of defibrotide in pediatric patients versus adult patients.*

**Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)**

The patients in this registry and data review were limited to first-time transplant recipients.

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

**Table 44 Demographics for CIBMTR Study**

<b>Baseline Characteristics</b>	<b>Defibrotide N=41 n(%)</b>	<b>Non-defibrotide N=55 n(%)</b>
<b>Year of Transplant</b>		
2008	5(12)	5(9)
2009	16(39)	29(53)
2010	14(34)	12(22)
2011	6(15)	9(16)
<b>Donor Type</b>		
Allogenic unrelated	36(88)	45(82)
Allogenic HLA-Matched	2(5)	7(13)
Autologous	2(5)	2(4)
Allogenic-syngeneic	0(0)	1(2)
Allogenic unrelated donor	1(2)	0(0)
<b>Graft Source</b>		
Cord Blood	22(54)	23(42)
Peripheral stem Cells	14(34)	22(40)
Bone Marrow	5(12)	10(18)
<b>End organ dysfunction manifestation</b>		
Renal dysfunction only	19(46)	31(56)
Pulmonary dysfunction only	12(29)	18(33)
Renal and pulmonary	10(24)	6(11)
<b>Time from HSCT to VOD Diagnosis</b>		
Mean number of day	17(8)	21(18)
Median(range)	14(4,37)	14(2, 85)

The most common underlying disease leading to HSCT was acute myelogenous leukemia with 12 patients (29%) in the defibrotide group and 19(34%) in the non-defibrotide group. The other common primary diseases included ALL 6(15%) and 11(20%), MDS/MPV 5(12%) and 10(18%) for the defibrotide and non-defibrotide group, respectively.

The two groups were well matched with regard to disease status at time of transplant with regard to disease in remission versus non-remission as well as non-malignant diseases.

In the defibrotide group more patients received GvHD prophylaxis regimens with cyclosporine (defibrotide 54%; non-defibrotide 40%). More patients in the non-defibrotide group (57%)

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

received GvHD prophylaxis with tacrolimus and sirolimus compared to the defibrotide group (41%). The use of sirolimus was similar between the two groups (defibrotide 15%; non-defibrotide 9%).

Myeloablative regimens were higher in the defibrotide group (88%) compared to 75% in the non-defibrotide group. Busulfan based myeloablative regimens were higher in the defibrotide group (51%) compared to the non-defibrotide group (36%).

*Reviewer Comment: There was an imbalance in some of the demographic factors that would possibly confer a survival advantage in the non-defibrotide group. These include lower incidence of pulmonary and renal dysfunction at baseline, lower number of myeloablative regimens (75%) in the non-defibrotide compared to the defibrotide group (88%). More busulfan (51%) containing regimens in the defibrotide group compared to the non-defibrotide group (36%). In general, pulmonary and renal dysfunction at baseline portends a worse prognosis in patients with hepatic VOD. Myeloablative regimens and in particular busulfan related regimens are associated with worse survival in patients undergoing transplantation. Despite the retrospective nature of study and small numbers, there is still a trend toward survival seen in the defibrotide group despite the fact that the non-defibrotide arm had more patients with factors associated with potential survival advantage.*

*Overall, the population in the treatment arm and standard of care arm are similar to the treatment arm and historical control in Study 2005-01.*

### **Treatment Compliance, Concomitant Medications, and Rescue Medication Use**

Not applicable as this is a retrospective review of CIBMTR registry database.

### **Efficacy Results - Primary Endpoint**

Day + 100 survival post-HSCT was evaluated. This endpoint was a binary outcome of patients either dead or alive at Day + 100 post-HSCT. The observed Day + 100 post-HSCT survival rates were 39% and 31% for defibrotide and non-defibrotide patients, respectively.

**Table 45 Survival at Day + 100 Post-HSCT (Reviewer Table)**

<b>Patients alive at Day + 100 post-HSCT</b>	<b>Defibrotide N=41</b>	<b>Non-Defibrotide N=55</b>
n(%)	16(39)	17(31)
(95% CI)	(24-56)	(19-45)

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

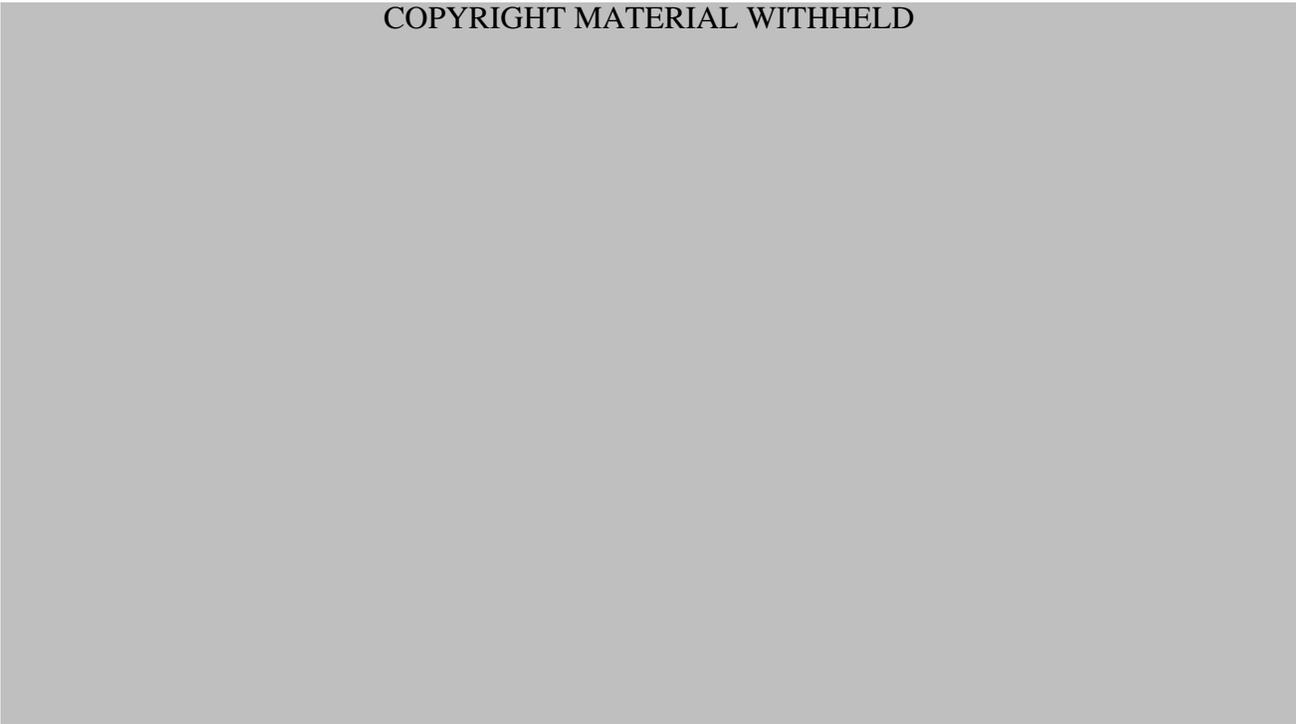
*Reviewer Comment: The Day + 100 survival rate of 39% in the defibrotide group is similar to the survival rate in the treatment arm of Study 2005-01(38%). The survival rate in the non-defibrotide group of 31% is higher than what was seen in historical control arm of Study 2005-01(25%).*

The Kaplan-Meier Probability of Survival at Day + 100 post-HSCT is displayed in the table below. The CSR references the CIBMTR as source of figure.

**Figure 6 Kaplan-Meier Probability of Survival at Day + 100 post-HSCT**

**Source: Applicants CSR Module 5.3.5.2 page 37**

COPYRIGHT MATERIAL WITHHELD



*Reviewer Comment: The numerical improvement in survival in the defibrotide arm of 39% is similar to the numerical improvement in survival from the pivotal study for the defibrotide arm (38%). Although the patient level data was not reviewed for this registry study, the survival observed in the defibrotide arm provides additional compelling evidence of the effectiveness of defibrotide.*

Clinical Review  
 Tanya Wroblewski, M.D.  
 Donna Przepiorka, M.D. Ph.D.  
 NDA 208114  
 Defitelio (Defibrotide Sodium)

The Day + 100 survival post-HSCT in age groups are described in the table below.

**Table 46 Survival at Day + 100 post-HSCT by Age Group (Reviewer Table)**

<b>Patients Alive at Day + 100 post-HSCT</b>	<b>Defibrotide N=41</b>	<b>Non-Defibrotide N=55</b>
<b>Age &lt;16 years n(%)</b>	N=25	N=11
Patients alive n(%) (95% CI)	10(40) (21-61)	5(46) (17-77)
<b>Age &lt;16 years n(%)</b>	N=16	N=44
Patients alive n(%) (95% CI)	6(38) (15-65)	12(27) (15-43)

*Reviewer Comment: Despite more pediatric patients in the defibrotide arm the survival of pediatric patients was slightly higher in the non-defibrotide arm. The survival of pediatric patients compared to adult patients in the defibrotide arm was comparable. Any definitive conclusions are difficult to conclude regarding pediatric subgroup due to the small numbers and retrospective nature of registry study.*

**Data Quality and Integrity - Reviewers' Assessment**

The trial is a registry review. There were no conduct issues that might influence the efficacy results.

**Efficacy Results - Secondary and other relevant endpoints**

VOD Resolution at Day + 100 post-HSCT was also evaluated. The observed VOD resolution rate at Day + 100 post-HSCT was 51% for the defibrotide group and 29% for the non-defibrotide group. Resolution of VOD was based on investigator’s response to Question 470 on CIBMTR form 2100(Did VOD resolve by Day + 100?).

**Dose/Dose Response**

Not Applicable

**Durability of Response**

Not applicable

**Persistence of Effect**

Not Applicable

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

### **Additional Analyses Conducted on the Individual Trial**

No additional analyses of Study CIBMTR were performed.

## **6.4. Study 2006-05**

### **6.4.1. Study Design**

#### **Overview and Objective**

Study 2006-05 is entitled, “Defibrotide for Patients with Hepatic Venous-occlusive Disease (VOD): A Treatment IND Study”. The main objective of this treatment IND is to provide defibrotide under 21 CFR 312.34 (“Treatment Use of an Investigational New Drug”). This IND also collected additional information to include usage, tolerability, and safety data from patients with a diagnosis of hepatic VOD (either following HSCT or chemotherapy) with or without organ dysfunction treated with defibrotide.

#### **Trial Design**

Study 2006-05 is an ongoing multicenter, single arm, open-label expanded access study to provide defibrotide (25 mg/kg/day) to patients diagnosed with VOD. All patients are to receive 25 mg/kg/day of defibrotide with the recommended minimum treatment duration of 21 days. Patients are recommended to continue treatment until they achieve a complete response or discharged from the hospital. It is estimated that based on prior experience the longest duration of therapy would be approximately 80 days.

#### **Inclusion Criteria**

VOD Diagnosis made by the Baltimore Criteria, Modified Seattle Criteria or biopsy proven:

- Baltimore Criteria: Bilirubin  $\geq$  2 mg/dL and at least 2 of the following
  - Ascites (radiographic or physical exam)
  - Weight gain  $\geq$  5% above baseline weight (defined as weight on the first day of conditioning- if this value is not available, the weight on the day of admission to the HSCT unit may be used)
  - Hepatomegaly increased over baseline
- Modified Seattle Criteria (McDonald et al 1984) At least two of the following:
  - Bilirubin  $\geq$  2 mg/dl
  - Ascites (radiographic or physical exam) and/or weight gain  $\geq$  5% above baseline weight
  - Hepatomegaly increased over baseline
- Patients who do not meet the Baltimore Criteria or Modified Seattle Criteria and have biopsy proven VOD are eligible

## Clinical Review

Tanya Wroblewski, M.D.

Donna Przepiorka, M.D. Ph.D.

NDA 208114

Defitelio (Defibrotide Sodium)

## Exclusion Criteria

- Clinically significant uncontrolled acute bleeding, defined as hemorrhage requiring > 15 cc/kg of packed red blood cells to replace blood loss, or bleeding from a site which in the Investigator's opinion constitutes a potential life-threatening source irrespective of amount of blood at any point from the date of SCT through the date of VOD diagnosis.
- Hemodynamic instability as defined by a requirement for 2 or more vasopressors(not including renal-doses of dopamine) or inability to maintain mean arterial pressure with single vasopressor support
- Use of any medication which increased the risk of hemorrhage. Use of heparin or other anticoagulants within 12 hours of defibrotide therapy initiation, except for routine central line venous line management, fibrinolytic instillation for central venous line occlusion, intermittent dialysis or ultrafiltration of continuous veno-venous hemodialysis.
- Women who are pregnant

## Procedures

Multi-organ failure is not required for eligibility however information regarding renal and pulmonary function must be collected at study entry and assessed throughout the time that the patient is on Defibrotide therapy.

- A patient will be considered to have pulmonary dysfunction (either at study entry or anytime while on study) should the patient have either: documentation of oxygen saturation < 90% on room air or requirement for oxygen supplementation/ventilator dependence. Dysfunction must be attributable to fluid overload or mechanical impingement from abdominal distention or hepatic enlargement and not to an infectious cause.
- A patient will be considered to have renal dysfunction should the patient have either serum creatinine  $\geq 3$  x value on the date of admission to the SCT unit for conditioning or  $\geq 3$ x lowest valued during conditioning prior to SCT or chemotherapy or creatinine clearance or GFR < 40% of admission value or dialysis dependence. Renal dysfunction must be attributable to VOD and not to an alternate cause.

While patient remains on defibrotide therapy, the patient should undergo daily assessment of bilirubin, fibrinogen, BUN, serum creatinine, CBC and platelet count, prothrombin time and partial thromboplastin time.

- Daily assessments of potentially drug-related toxicity
- Follow-up: Patients initiating defibrotide following SCT are required to return to clinic on Day + 30 and Day + 100 following SCT; survival and complete response will be determined

## Clinical Review

Tanya Wroblewski, M.D.

Donna Przepiorka, M.D. Ph.D.

NDA 208114

Defitelio (Defibrotide Sodium)

### Discontinuation Criteria:

- After at least 21 days of therapy, defibrotide may be discontinued for patients who have achieved a CR.
- Defibrotide should be discontinued if significant bleeding occurs.
- Defibrotide may be held for surgical procedures or to accommodate other urgent medication without necessitating dose modification
- Defibrotide should be discontinued for grade 3 or 4 toxicity. Patients may have a single attempt at re-challenged if the toxicity resolves.

### Concomitant Therapy

During therapy it is recommended that platelets be kept  $> 30,000/\text{mm}^3$ , HCT  $> 30\%$  with transfusion, INR  $< 1.5$  and fibrinogen  $> 150 \text{ mg/dL}$  with factor replacement as necessary. Concomitant ursodiol is allowed and patients may not be treated concurrently with medications that increase the risk of hemorrhage, such as warfarin, NSAIDs, heparin or systemic t-PA.

### Safety

All adverse events whether or not they are serious or expected will be recorded on the Case Report Forms (CRFs). The NCI's Common Terminology Criteria for Adverse Events Version 4.0 will be used where applicable.

### Study Endpoints

Survival by Day + 30 and Day + 100 (post-HSCT or following the start date of chemotherapy), as applicable were considered both an efficacy and safety assessment for Study 2006-05. Additional efficacy data (Complete Response by Day + 30 and Day + 100 post-HSCT or following the start date of chemotherapy as applicable) were captured on case report forms, were not included in the interim study report submitted by the Applicant.

Limited laboratory data (primary total bilirubin and serum creatinine) were collected as part of this study for the primary purpose of supporting VOD diagnosis and outcome assessment but no planned lab data evaluations from this study.

### Statistical Analysis Plan

All descriptive statistical analyses were performed using SAS statistical software Version 9.3 or higher unless otherwise noted. Adverse events were coded using the MedDRA Version 16.0. A description of the populations is below:

## Clinical Review

Tanya Wroblewski, M.D.

Donna Przepiorka, M.D. Ph.D.

NDA 208114

Defitelio (Defibrotide Sodium)

- All patient population: All patients enrolled in Protocol 2006-05 as of 31 December 2013 including data that were collected through to the date of the database snapshot of 5 December 2014.
- Intent-To-Treat(ITT) Efficacy Population(VOD with MOF): Patients included in all patients population who were diagnosed with VOD associated with renal or pulmonary organ dysfunction and who had documentation of receiving at least one dose of defibrotide, as determined by any of the following variables: start date, total days, or total doses
- VOD Population: Patients included in the all patients population who were diagnosed with VOD(with or without MOF) who had documentation of receiving at least one dose of defibrotide as determined by : start date, total days or total doses
- Safety Population: All patients who had documentation of receiving at least one dose of study drug as determined by start date, total days or total doses.

*Reviewer Comment: The ITT Efficacy Population is comprised of patients who received high dose chemotherapy and transplantation as well as chemotherapy alone. The indication population consists of patients who received high dose chemotherapy and transplantation which is a subset of the ITT efficacy population. This population is similar to the treatment arm in Study 2005-01.*

The primary efficacy variable for the interim report is survival by Day + 100 following HSCT or start of chemotherapy. For this binary outcome, dead/alive at Day + 100 data were presented in terms of the proportions alive a day + 100(point estimates) together with 95% confidence intervals (CIs). A tolerance window of +/- 7 days for Day + 100 survival information was considered in the proportion calculation. Kaplan-Meier curves were presented to describe the distributions of time to death by Day + 100.

The definition of CR will vary by entrance criteria:

CR rate for patients with VOD by Baltimore criteria: CR will be defined as the percentage of patients who after meeting study entry criteria have the following characteristics: bilirubin < 2mg/d, and if present at study entry or present at any time on study, MOF has resolved.

CR rate for patients with VOD by modified Seattle Criteria CR will be defined as the percentage of patients who after meeting study criteria have the following characteristics1) bilirubin < 2mg/dL and if present at study entry or present at any time on study, MOF has resolved. For those patients who qualified for the study by VOD without Hyperbilirubinemia, resolution of other symptoms of VOD is required.

If present at the start of study, resolution of MOF is necessary to define the patient as having a complete response.

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

- Resolution of renal dysfunction is defined as: serum creatinine < 1.5 times baseline or the upper limit of normal for the patient’s age and CrCl and/or GFR > 80% of admission value AND for patients who were dialysis dependent at study entry or because dialysis dependent at any pint during the study, resolution of renal dysfunction is defined as independence form dialysis
- Resolution of pulmonary dysfunction is defined as documentation of oxygen saturation > 90% at least one hour apart and oxygen supplementation no longer required and resolution of ventilator dependence. Resolution of oxygen requirement must be stable for at least 24 hours before it will be considered indicative of complete response.

The Safety Population was used for the safety evaluations. Only TEAEs were presented in the analysis tables. The number of patients reporting TEAEs was tabulated by MedDRA primary SOC and PT frequency of occurrence for the following: All events, Grade 3/4/5 events, all treatment related adverse events, Grade 3/4/5 treatment related events, treatment related events leading to discontinuation.

**Table 47 Protocol Amendments**

<b>Date</b>	<b>Amendment</b>	<b>Key Changes in Protocol</b>
17 December 2007	Amendment 1	Clarified AEs and outcome data to be collected on Day + 30 and day + 100 post HSCT Increased consistency with the Phase 3 pivotal study(protocol 2005-01) with regard to the criteria to define CR.
12 August 2009	Amendment 2	Modified eligibility requirement by removing: the requirement for patients to demonstrate MOF prior to enrollment and the requirement for patients to be eligible only following HSCT-patients could meet eligibility criteria following chemotherapy  Requirement for VOD before Day + 35 and MOF by Day + 45 removed allowing patients with late onset VOD to be treated  Induced a cost recovery program
11 August 2010	Amendment 3	New formulation introduced  Reintroduce the comparison of the HC arm of the Phase 3 study 2005-01 and patients enrolled under Protocol 2006-

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

		05 who met eligibility criteria of Protocol 2005-01 regarding Day + 100 survival and CR  Allowed increased number of enrolled patients
3 March 2011	Amendment 4	Added pregnancy to contraindications to the use of defibrotide  Allowed enrollment of patients with VOD diagnosis based on modified Seattle Criteria in addition to those fulfilling Baltimore criteria (elevation of total bilirubin to 2mg/dL or higher was no longer mandatory)  Increased enrollment from 200-300 to 600 patients

#### **Data Quality and Integrity: Sponsor's Assurance**

The Sponsor focuses data quality assurance measures on key parameters for the ongoing study. The Applicant conducted limited on-site monitoring activities and implemented data management efforts to verify and query data. Information on SAEs was submitted by sites to the Sponsor's Drug Safety Department into the safety database. Study Results

#### **Compliance with Good Clinical Practices**

The study report for 2006-05 included a statement that the trial is being conducted in accordance with the Declaration of Helsinki and Good Clinical Practice.

#### **Financial Disclosure**

The Applicant has adequately disclosed financial interests/arrangements with clinical investigators. The financial disclosure information does not raise questions about the integrity of the data. See Appendix 13.2 of this review for details of the financial disclosure information.

#### **Patient Disposition**

The study is ongoing at the time of this report and open to enrollment at approximately 90 sites. The data represents an interim analysis of data collected from 78 sites in the United States in patients enrolled up to 31 December 2013 with all data reported through a data cut-off of 31 December 2014. As of 31 December 2013, 681 patients have received treatment with defibrotide.

Of the 681 patients enrolled across 78 centers in the US, 649 patients have documented evidence that defibrotide was administered and are included in the Safety Population. From the 78 centers that enrolled patients, 41 centers enrolled < 5 patients each.

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

Of the total of 681 patients enrolled in the study as of the cut-off date of 31 December 2013, there was incomplete data for 39 patients so the VOD population consists of 648 patients who have documentation of receiving at least one dose of defibrotide. Within this VOD population, 255 did not develop MOF and 387 patients had VOD with MOF. The ITT Efficacy Population consists of 387(57%) patients (VOD with MOF). Within the ITT efficacy population, 351(91%) underwent HSCT and 36(9%) received chemotherapy prior to developing VOD. The following table describes the demographics for the entire study populations for Study 2006-05.

**Table 48 Study Populations for Study 2006-05**

<b>Variable n(%)</b>	<b>Defibrotide N=681</b>
All patients	681(100)
<b>Treated with defibrotide</b>	
Yes	649(95)
No	32(5)
<b>Safety Analysis Population</b>	649(95)
Stem Cell Transplant	579(89)
Chemotherapy	70(11)
<b>ITT Efficacy Population</b>	387(57)
Stem Cell Transplant	351(91)
Chemotherapy	36(9)
<b>VOD Population</b>	642(94)
Stem Cell Transplant	573(89)
Chemotherapy	69(11)

*Reviewer Comment: The indication population consists of patients diagnosed with severe hepatic VOD with multi-organ failure after HSCT. This comprises 351 patients /681(52%) and is the population used for the primary efficacy analyses of Day + 100 survival post-HSCT.*

### **Protocol Violations/Deviations**

There were 30 protocol deviations reported from monitoring visit reports related to the ICF. The protocol deviations included the following:

- ICD not obtained prior to screening for 20 patients
- Nine patients signed incorrect versions of the informed consent form(ICF)
- The original signed and dated ICF and HIPAA forms for one patient were lost and no photocopies were available.

There were 2 deviations related to study drug that were considered critical:

- 2 patients were administered one dose each of expired study drug

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

There was a procedure-related deviation in 1 patient that was considered a critical protocol violation

- Study drug dosage recorded as wrong concentration

There were 4 protocol violations involving administration of disallowed concomitant medications to include 2 patients receiving low dose heparin and two patients received antithrombin-III during treatment with defibrotide.

Lastly there were 2 protocol violations including one patient receiving defibrotide under an emergency protocol but emergency use was not approved by Gentium or FDA and the patient subsequently consented and enrolled on the Treatment IND 2006-05. One patient experienced an SAE that was not reported within 24 hours of site staff becoming aware of the event.

*Reviewer Comment: The protocol deviations are not substantial to warrant concern regarding the interoperability of the data.*

### Table of Demographic Characteristics

A summary of the study population for the ITT Efficacy population and the entire safety population are provided in the table below. The majority of patients in the ITT efficacy and safety populations were male (53% and 56%, respectively). The majority of patients in the ITT efficacy population and safety populations were less than or equal to the age of 16 years (57% and 59%, respectively) at the time they received the HSCT/chemotherapy. The majority of the pediatric population in the ITT Efficacy and Safety Populations consisted of children from 2-11 years (53% and 53%, respectively).

**Table 49 Baseline Demographic Variables for Study 2006-05**

Variable	ITT Efficacy Population (N=387) n(%)	Safety Population (N=649) n(%)
<b>Gender</b>	203(53)	365(56)
Male	184(48)	284(44)
Female	184(48)	284(44)
<b>Race</b>		
White	258(67)	422(65)
Non-white	129(33)	227(35)
<b>Age of time of HSCT/Chemo(years)</b>		
Median	14	14
Range	0.1, 69	0, 69
<b>Age</b>		
< 16 years	219(57)	380(59)
>16 years	168(43)	269(41)

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

Variable	ITT Efficacy Population (N=387) n(%)	Safety Population (N=649) n(%)
<b>Pediatric Class</b>		
Infant and Toddler(0-23 months)	56(26)	104(27)
Children, 2-11 years)	117(53)	200(53)
Adolescent, 12-16 years	46(21)	76(20)
<b>Weight(baseline) kg</b>		
Median	51	48
Range	3.2, 135	3.0, 135

**Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)**

The most common baseline disease was AML followed by ALL for the ITT Efficacy Population and the Safety Population. The most commonly reported GvHD prophylaxis in both the efficacy and safety population was tacrolimus. Table 50 describes the baseline characteristics.

**Table 50 Baseline Disease Characteristics**

Variable	ITT Efficacy N=387 n(%)	Safety Population N=649 n(%)
<b>Primary Disease</b>		
AML	107(28)	174(27)
ALL	96(25)	149(23)
Other	79(21)	137(21)
Neuroblastoma	26(7)	48(7)
MDS	20(5)	34(5)
NHL	16(4)	31(5)
Other leukemia	14(4)	24(4)
Immunodeficiency	10(3)	19(3)
CML	10(3)	13(2)
<b>Type of HSCT</b>		
Allograft	317(90)	503(88)
Autograft	24(10)	68(12)
<b>GVHD prophylaxis</b>		
Tacrolimus	166(43)	503(88)
Cyclosporine	118(31)	191(30)
Methotrexate	111(29)	189(29)
Sirolimus	47(12)	64(10)
Other	112(29)	186(29)
None	80(21)	152(23)

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

The most commonly reported conditioning regimens administered to patients in the ITT efficacy included cyclophosphamide (64%), busulfan (44%) and total body irradiation (36%). Fludarabine was reported in 24% and melphalan (18%), all other regimens were reported as less than 20%.

Additional analyses of the diagnosis of VOD and MOF was performed in the ITT Efficacy Population and included the diagnosis of VOD and MOF at screening, date of diagnosis and qualifying criteria. The majority of patients in the ITT Efficacy Populations were diagnosed with VOD post-HSCT (91%). Only a small proportion of patients had VOD diagnosed after receiving chemotherapy alone (9%).

The most common VOD diagnostic criteria reported in patients included bilirubin > 2mg/dL, ascites and weight gain > 5%. The majority of patients in the ITT Efficacy population qualified with a diagnosis of VOD based on the Baltimore Criteria (87%).

**Table 51 Additional Demographic Data for Study 2006-05**

<b>Variable</b>	<b>ITT Efficacy (Severe VOD with MOF) N=387 n(%)</b>	<b>Safety Population N=649 n(%)</b>
Diagnosis of VOD, n	387	642
Post-HSCT	251(91)	573(89)
Post-chemotherapy	36(9)	69(11)
Onset day of VOD post- HSCT/chemotherapy		
Median	15	15
Range	-33, 316	-33, 456
<b>VOD Criteria, n(%)</b>		
Bilirubin > 2mg/dL	352(91)	576(90)
Ascites	341(88)	561(87)
Weight Gain > 5%	345(89)	553(86)
Hepatomegaly	278(72)	473(74)
<b>Diagnosis based on Baltimore criteria</b>	336(87)	538(84)
<b>Diagnosis based on Modified Seattle Criteria</b>	29(8)	76(12)
<b>Diagnosis based on biopsy proven VOD, n (%)</b>	22(6)	28(4)

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

Variable	ITT Efficacy (Severe VOD with MOF) N=387 n(%)	Safety Population N=649 n(%)
<b>Any multi-organ failure criteria, n (%)</b>		
Yes	387(100)	387(60)
No	0(0)	255(39)
Multi-organ Failure, n (%)		
Renal dysfunction	236(61)	238(37)
Serum creatinine > 3 x	193(50)	194(30)
Creatinine clearance or GFR < 40%	78(20)	78(12)
Dialysis Dependence	105(27)	106(17)
Pulmonary Dysfunction, n(%)	299(77)	300(47)
Oxygen saturation, 90%	145(38)	145(23)
Oxygen supplementation	302(78)	303(47)
Ventilator dependence	135(35)	137(21)

In total, 14 patients had onset of VOD > 100 days post-HSCT/chemotherapy and one patient was reported as having onset of VOD 33 days prior to undergoing HSCT. The majority of patients had VOD diagnosis based on the Baltimore Criteria.

#### **Treatment Compliance, Concomitant Medications, and Rescue Medication Use**

The study drug is infused intravenously under the supervision of health professionals, compliance is not considered an issue in this study.

#### **Efficacy Results - Primary Endpoint**

The indication population (N=351) includes subject with VOD [REDACTED] <sup>(b) (4)</sup> following HSCT. The Day + 100 survival for this population is 45% (95% CI, 45-56).

Among the entire ITT Efficacy population of patients (n=387) with VOD and MOF, 183(47%) were alive at Day + 100 post-HSCT or chemotherapy. The Day + 100 status was not available for 17 patients (4%). Table 52 describes Day + 100 survival for the indication Population and ITT Efficacy Population and the entire Defibrotide Population.

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

**Table 52 Day + 100 Survival post HSCT for Indication Population and ITT Efficacy Population and entire VOD Population**

Category	Defibrotide (Post-HSCT with severe MOF) Indication Population N=351	Defibrotide (post-HSCT + chemo with severe MOF) N=387	Defibrotide (entire VOD population +/- MOF) N=642
<b>Survival by Day + 100</b>			
Alive, n(%)	159(45)	183(47)	337(53)
95% CI	40-51	42-52	49-56
Death, n(%)	178(51)	187(48)	273(43)
95% CI	46-56	43-53	39-46
Day + 100 status not available, n(%)	14(4)	17(4)	23(5)

*Reviewer Comment: The small number of patients who developed severe VOD with MOF after chemotherapy alone (N=36) is too small to draw any conclusions about efficacy in this population.*

#### **Data Quality and Integrity - Reviewers' Assessment**

This is an expanded access study. No trial design or conduct issues that might influence the efficacy results were discovered.

#### **Efficacy Results - Secondary and other relevant endpoints**

The secondary efficacy parameters such as complete response were not evaluated in this analysis.

#### **Dose/Dose Response**

Not applicable

#### **Durability of Response**

Not applicable.

#### **Persistence of Effect**

Not applicable.

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

### **Additional Analyses Conducted on the Individual Trial**

There were no additional analyses conducted on Study 2006-05.

## **6.5. Study 2004-000592-33 (hereafter Study 2004)**

### **6.5.1. Study Design**

#### **Overview and Objective**

Study 2004 is a Phase 3, multi-center, prospective, randomized, open-label, controlled study for the prophylactic use of defibrotide for the prevention of hepatic VOD in high-risk pediatric patients following HSCT. Patient randomized to receive defibrotide at a fixed dose of 25 mg/kg/day and patients randomized to the control arm received standard of care after HSCT. Patients were evaluated for VOD up to Day + 30 post-HSCT. The primary efficacy endpoint for this study was the incidence of VOD by Day + 30 post-HSCT (by modified Seattle Criteria).

#### **Trial Design**

Study 2004 was an open-label, multi-center, randomized, controlled Phase 3 clinical trial to evaluate the efficacy and safety of prophylactic defibrotide versus no prophylactic treatment in pediatric patients < 18 years of age undergoing HSCT at high risk for developing VOD. Randomization was stratified by center and the diagnosis of osteopetrosis (yes/no).

Patients in the defibrotide prophylaxis group received defibrotide intravenously at 6.25 mg/kg every 6 hours for a total daily dose of 25 mg/kg. Patients in the defibrotide prophylaxis arm received their first dose of defibrotide on the day of conditioning and treatment was to be continued until Day + 30 post-HSCT or until the patient was discharged from the hospital. The control arm received only post-transplantation standard of care at the site. The study protocol allowed for rescue defibrotide for patients in the control arm who developed VOD at a dose of 25 mg/kg/day IV in 4 doses beginning on the day of diagnosis and ending on complete resolution of symptoms.

Eligible patients were < 18 years of age undergoing allogeneic or autologous HSCT with preceding myeloablative chemotherapy and who had at least one of the following high-risk criteria: pre-existing liver disease, second myeloablative HSCT, history of treatment with gemtuzumab ozogamycin, allogeneic HSCT or leukemia beyond second relapse, osteopetrosis, conditioning with busulfan and melphalan or macrophage activating syndromes.

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

Table 53 Schedule of Assessments for Study 2004

Procedure	Study Entry	Prior to HSCT	HSCT Day+0	Day+30 Post-HSCT	Day+100 Post-HSCT	Day+180 Post-HSCT
Informed Consent; Eligibility Review	X					
Pregnancy Test (if indicated)	X					
Registration and Randomization	X					
Medical History <sup>a</sup>	X					
Performance Status <sup>b</sup>	X			X	X	X
Weight	X	X	X	[X] <sup>c</sup>		
Abdominal Ultrasound <sup>d</sup>	X			[X] <sup>c</sup>		
Defibrotide or no VOD prophylaxis <sup>e</sup>		X	X	X <sup>e</sup>		
Conditioning Regimen <sup>f</sup>		X				
HSCT <sup>g</sup>			X			
Engraftment Assessment				X	X	
Systemic Complications <sup>h</sup>				X	X	X
VOD Assessment <sup>i</sup>				X	X	X
GvHD Assessment				X	X	X
TTP Assessment <sup>j</sup>						X
Relapse of Underlying Disease				X	X	X
Concomitant Medications	X	X	X	X	X	X
Adverse Events		X	X	X	X	X
AST, ALT, AP, GGT	X			[X] <sup>c</sup>		
Clinical Labs <sup>k</sup>		X		X	X	X
Special Studies <sup>l</sup> and PAI-1 <sup>m</sup>		X		X	X	X
Mortality/Survival		X	X	X	X	X

<sup>a</sup> For patients with underlying malignancy, details of prior chemotherapy and histological subtype were required. For all patients, assessment of prior liver disease, coagulopathy, and systemic viral infections was required.

<sup>b</sup> Karnofsky scale ( $\geq 16$  years) or Lansky scale ( $< 16$  years), as appropriate.

<sup>c</sup> Performed if VOD suspected or diagnosed

<sup>d</sup> At Baseline for all patients, with assessment of liver size, ascites, gallbladder wall thickness, and flow pattern in hepatic and para-umbilical veins.

<sup>e</sup> For patients in the defibrotide arm who did not develop symptoms of VOD, defibrotide was continued until Day+30 or discharge from inpatient care (with a minimum treatment of 14 days). For patients in either arm with a diagnosis of VOD, defibrotide was continued until complete resolution of symptoms.

<sup>f</sup> Patients in the defibrotide prophylaxis arm received their first dose of defibrotide on the day of conditioning (prior to conditioning). Details of conditioning regimen (drugs, doses, route of administration) and type of immunosuppression were collected.

<sup>g</sup> Details on type and source of graft.

<sup>h</sup> Assessment of post-HSCT complications (pulmonary, bacterial, viral, fungal, hemorrhagic cystitis, capillary leakage syndrome and other complications). Day+180: plus neurological, hepatic, renal, endocrine, cerebral, ophthalmologic complications.

<sup>i</sup> Patients with suspected VOD: ultrasound assessment, maximum weight, aspartate transaminase (AST), alanine transaminase (ALT), creatinine, bilirubin, increased requirement for platelet transfusions, bimodal presentation of VOD, portal vein thrombosis, peripheral edema, encephalopathy, renal failure, need for dialysis, oxygen and/or assisted ventilation, ICU admission, replacement of coagulation factors. Liver biopsy, if indicated.

<sup>j</sup> TTP was assessed from study entry up through Day+180. Details on consumptive coagulopathy, late onset consumptive anemia, late onset increased blood urea nitrogen (BUN)/creatinine, weight gain and poor urine output, fragmented RBCs, late onset pathological urine analysis, encephalopathy.

<sup>k</sup> WBC, platelets, bilirubin. Prior to HSCT and weekly until D+100 or discharge.

<sup>l</sup> Factor VIII, Protein C, AT III, PT, PTT, fibrinogen, Protein S. Prior to HSCT and weekly until D+100 or discharge.

<sup>m</sup> PAI-1 (optional test). Prior to HSCT and weekly until D+100 or discharge.

ALT = alanine transaminase (SGPT); AP = alkaline phosphatase; AST = aspartate transaminase (SGOT);

GGT = gamma-glutamyl transferase; GvHD = graft versus host disease; HSCT = hematopoietic stem cell transplant; TTP = thrombotic thrombocytopenic purpura; VOD = veno-occlusive disease

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

## **Study Endpoints**

The primary endpoint is the incidence of VOD by Day + 30 post-HSCT using modified Seattle Criteria. The secondary efficacy endpoint is the composite score of VOD severity composed of the incidence of multi-organ failure (MOF) by Day+100 and survival through Day + 100.

## **Statistical Analysis Plan**

The sample size calculation was not performed at the start of the trial because the effect size was not known. A first approximation, a sample size of 121 evaluable patients per group was estimated to be needed based on respective VOD incidence of 30%(control arm and 15%(defibrotide prophylaxis arm), a one-sided 0.025 level of significance(or two-sided 0.05 level of significance) and 80% power. To determine if the sample size was reasonably accurate an adaptive interim analysis was conducted assess conditional power for a statistically significant result by the end of the study when 120 patients in each group completed the Investigators evaluation of primary outcome.

The DSMB concluded there were no significant safety concerns and no evidence of clinical futility and it was recommended that the sample size be increased to 180 patients per arm to achieve an 80% conditional power for detecting a statistically significant benefit for defibrotide over control.

The intent-to-treat analysis set is defined as all randomized patients. This is the primary analysis set with patients identified as having a competing risk.

The primary efficacy endpoint was the incidence of VOD by Day + 30 post-HSCT (determined by independent review committee [IRC] review and adjudication. The primary analysis was the Cumulative Incidence Competing Risks (CICR) analysis based on IRC adjudication of VOD. This analysis was conducted using the ITT and Per Protocol analysis sets. Treatments were compared on time to VOD, where all randomized patients who did not achieve VOD by Day + 30 were censored at Day = 30 or date of last known follow-up whichever was earlier. Death not due to VOD, discontinuing the study due to an AE and receipt for a second transplant due to failure of the first transplant were all considered competing risks in this analysis.

The secondary efficacy endpoint is the composite score composed of incidence of MOF by Day + 100 and survival through Day + 100.

## **Protocol Amendments**

A summary of the key protocol modifications made with each protocol amendment is described in the table below.

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

**Table 54 Protocol Amendments for Study 2004**

Date	Protocol Amendment	Description
2 February 2005	Amendment 1	Eligibility criteria modified and randomization and registration procedures updated.
28 March 2006	Amendment 2	DSMB established to monitor safety issues, diagnosis for osteopetrosis added as stratification factor, time period for VOD-associated MOF increased from Day +60 to Day + 100. Additional edits and clarifications
15 April 2008	Amendment 3	Primary efficacy endpoint modified from a composite score to including incidence of VOD, VOD –associated MOF and survival to “Incidence of VOD at Day + 30”. A blinded IRC was appointed to adjudicate the diagnosis of suspected VOD observed from HSCT through Day + 30. Methods of handling missing data added, previous primary efficacy endpoint(VOD composite score) retained as secondary endpoint. Adaptive interim analysis was clarified.

**Data Quality and Integrity: Sponsor's Assurance**

A comprehensive validation check program was used to verify the data, and discrepancy reports were generated accordingly for resolution by the Investigator. Accurate and reliable data collection was assured by verification and cross-check of the CRFs against the patient’s records by clinical monitors (100% source document verification was performed) and the maintenance of a drug-dispensing log by the study center.

The GCP Quality Audit by an independent, qualified CRO was also performed on 7 of the 28 participating centers. The highest accruing centers were preferentially selected for audit.

**6.5.2. Study Results**

**Compliance with Good Clinical Practices**

The Applicant provided attestation that this study was conducted in accordance with U.S. regulations governing the protection of human subjects, Institutional Review Boards, and the obligations of clinical investigators in accordance with good clinical practice (GCP).

**Financial Disclosure**

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

The Applicant submitted financial disclosure information from all investigators for this trial. No financial interests or arrangements were reported. Refer to appendix for financial disclosure information.

### **Patient Disposition**

A total of 364 patients were screened for the study. Eight patients were screen failures and the remaining 356 patients were randomized to the defibrotide prophylaxis arm(180 patients) or control arm(176) patients. Overall, 71% of patients completed the study through Day + 180, including 70% in the defibrotide prophylaxis arm and 72% in the control arm. Thirty percent of patients in the defibrotide group and 28% in the control arm withdrew from the study prematurely. The most common reasons in both group included death, lost to follow-up, adverse events and consent withdrawn.

### **Protocol Violations/Deviations**

There were 13 patients (8 defibrotide and 5 control patients) who failed to meet eligibility and entry criteria. Five patients in the prophylaxis arm and 4 in the control arm did not have myeloablative HSCT. Three patients did not meet high-risk VOD criteria (3 in the prophylaxis arm and 1 in the control arm). There were four patients (2 defibrotide and 2 control patients) who took excluded medications during the study with the most common being enoxaparin and ursodeoxycholic acid. There were 5 patients who had derivations in study procedures and 3 patients who had incorrect dosing of study drug.

**Table 55 Demographic Characteristics**

<b>Variable</b>	<b>Defibrotide Prophylaxis N=180</b>	<b>Control N=176</b>
Gender, n(%)		
Male	110(61)	101(57)
Female	70(39)	75(43)
Median Age at HSCT(years)(range)	5.0(0.2, 17)	4.0(0.1, 18)

In the prophylaxis group there were 46(26%) infants and toddlers, 91(51%) children age 2-11 and (43(24%) adolescents age 12-< 18 years of age. In the control arm there were 41(25%) infants and toddlers, 95(57%) children age 2-11 and 39(22%) adolescents age 12 to < 18.

### **Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)**

The most common underlying conditions in both study arms (defibrotide vs control) were AML (17% vs 24%), neuroblastoma (19% versus 18%), ALL(17% vs 24%) and myelodysplastic

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

syndrome(11% versus 6%).

The most frequently administered conditioning agents were busulfan and melphalan in both study arms. The most common GvHD prophylaxis medications received by patients in each treatment arm were cyclosporine A (55% vs 59%), anti-thymocyte globulin-rabbit (36% vs 46%) and methotrexate (32% vs 37%) in the defibrotide and control arms respectively.

Overall the VOD high-risk criteria were similar between patients in each treatment arm(defibrotide vs. control) with the most common conditioning with busulfan and melphalan (59% vs 56%), pre-existing liver disease(23% vs 31%) and second myeloablative HSSCT(14% vs 13%), respectively.

#### **Treatment Compliance, Concomitant Medications, and Rescue Medication Use**

Defibrotide is administered intravenously under the supervision of health professionals compliance is not considered an issue in this study.

#### **Efficacy Results - Primary Endpoint**

The primary efficacy endpoint of incidence of VOD by Day + 30 post-HSCT demonstrated that there were 22(12%) patients in the defibrotide prophylaxis arm compared with 35(20%) in the control arm who had a diagnosis of VOD by Day + 30. This results in a difference of 8%.

**Table 56 VOD Diagnosis Day + 30 Primary Endpoint ( FDA Statistical Review Team Table)**

<b>VOD Diagnosis day +30 to transplant</b>	<b>DF arm (N = 176)</b>	<b>Control arm (N = 180)</b>	<b>Total (N = 356)</b>
Yes	35 (19.9%)	22 (12.2%)	57 (16.0%)
No	136 (77.3%)	148 (82.2%)	284 (79.8%)
NA	5 (2.8%)	10 (5.6%)	15 (4.2%)

The Statistical team performed calculations taking into account missing data. Of note without missing data imputation, the Chi-square test of VOD diagnosis by Day + 30 in the treatment arm gives the p-value of (b) (4). With missing data imputation (assuming the patients with missing values are “no”), the chi-square test gives the p-value of (b) (4).

The Applicant also performed additional sensitivity analysis by the Applicant regarding missing data and counting missing data as failures results in a difference from 8% to 6%. VOD by Day = 30(missing data= VOD) in the prophylaxis arm is 31(17%) versus 40(23%).

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

*Reviewer Comment: The sensitivity analyses for missing data counting as failures leads to only a difference of 6% and a non-significant result. The small treatment effect from the primary analysis and small imbalance in missing data make this sensitivity analysis uninterpretable. Additionally, counting the missing data as failures may not be accurate representation of data. While the efficacy data demonstrates only a small difference there is still a positive signal that defibrotide may be beneficial in the prevention of VOD in appropriate population.*

**Data Quality and Integrity - Reviewers' Assessment**

The overall quality and integrity of the study was acceptable.

**Additional Analyses Conducted on the Individual Trial**

The Agency requested that the Sponsor conduct additional analyses regarding the incidence of VOD or Death by Day + 30 and Day + 100 post-HSCT in patients who meet high risk or very high risk entry criteria. This request was requested under IND 62118 as part of discussion of proposed prevention trial. The Applicant provided a cross reference letter to the IND in the NDA package. The following table describes the incidence of VOD or Death by Day + 30 or Day + 100 post-HSCT in patients at high risk or very high risk for VOD.

**Table 57 Incidence of VOD or Death by Day+30 and Day+100 Post- HSCT**

Patients from Study 2004-00592-33 Meeting High Risk or Very High Risk Entry Criteria (Applicant's Table)

	Day +30		Day +100	
	Defibrotide	Control	Defibrotide	Control
<b>N</b>	77	88	77	88
<b>VOD/Death</b>	9 (11.7%)	26 (29.5%)	15 (19.5%)	30 (34.1%)
<i>VOD</i>	8 (10.4%)	24 (27.3%)	8 (10.4%)	24 (27.3%)
<i>Death</i>	1 (1.3%)	2 (2.3%)	7 (9.1%)	6 (6.8%)
<b>No VOD/Alive</b>	68 (88.3%)	62 (70.5%)	62 (80.5%)	58 (65.9%)

*Reviewer Comment: The Applicant's analysis of the composite endpoint of incidence of VOD or death by Day + 30 in patients at high risk for VOD suggests a treatment effect for the prevention of VOD. The preliminary exploratory analysis supports the premise of a treatment effect of defibrotide in prevention of VOD in high risk or very high risk subjects. The difference in rates of*

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

*VOD between the defibrotide and control group also lends further clinical support to the role of defibrotide in the treatment of VOD.*

## 7 Integrated Review of Effectiveness

### 7.1. Assessment of Efficacy Across Trials

#### 7.1.1. Primary Endpoints

The primary efficacy endpoint most pertinent to this NDA review is Day + 100 survival post-HSCT for the treatment of severe VOD with multi-organ dysfunction. The pivotal trial, 2005-01, provides the basis for survival data with supporting Day + 100 survival after transplantation from three additional trials (Study 99-118, Study 2006-05 and the registry study CIBMTR). The following table provides a high level overview of the efficacy studies that support the primary efficacy endpoint of Day + 100 survival.

**Table 58 High-Level Description of Studies Supporting Efficacy Claim**

Study Elements	Study 2005-01	Study 99-118	Study 2006-05	CIBMTR Registry
Phase	3	2	3	Registry
Design	Open-label, single treatment arm vs untreated historical control	Randomized, open-label, 2 treatment arm, dose-comparison	Open-label, single treatment arm Treatment IND(ongoing)	Registry Database
Location	International	US	US	US
Number of Sites	34	9	78	54
Number of patients (daily dose)	102 (25 mg/kg/day)	149 25 mg/kg/day: 74 40 mg/kg/day:75	679 (25 mg/kg/day)	96 total (41 defibrotide and 55 non-defibrotide)

A side by side analysis of these four studies was performed and is detailed in Table 58. Only the ITT Efficacy Indication Population from Study 2006-05(VOD with MOF, n=351) is displayed in the table below. Of note patients in Study CIBMTR may overlap with Study 2006-05 due to the timing of each of these trials.

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

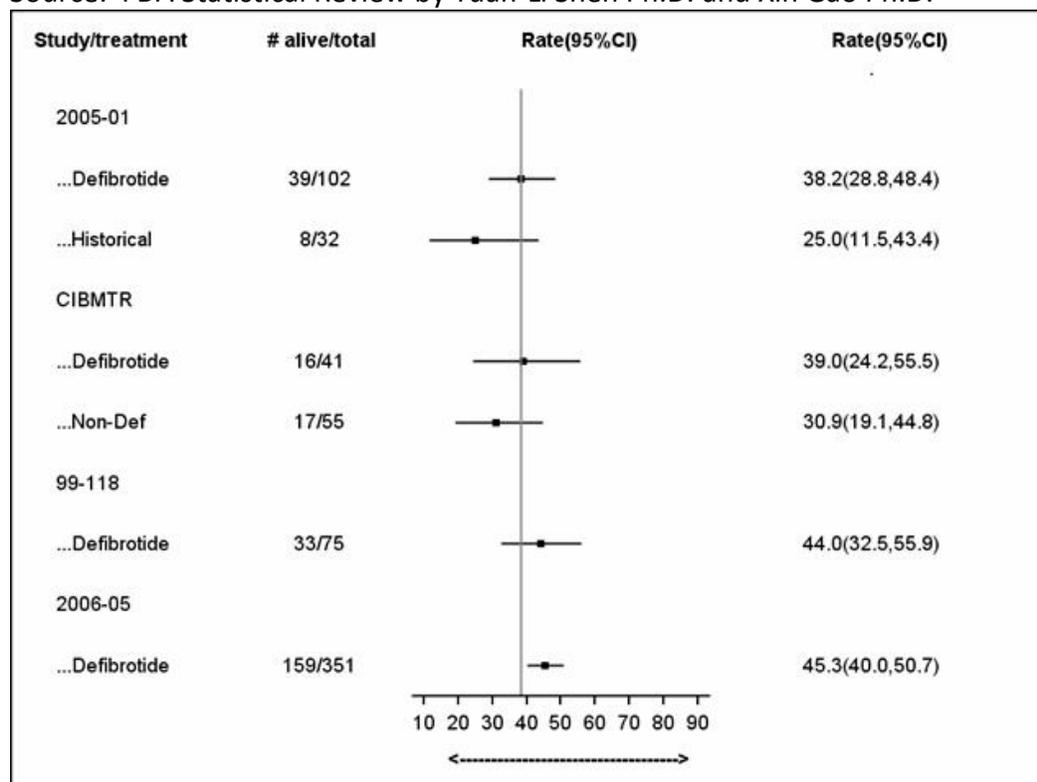
**Table 59 Day + 100 Survival post-HSCT across key efficacy studies**

Status, n(%)	Study 2005-01 Treatment Group N=102	Study 99-118 N=75	Study 2006-5 N=351	Study CIBMTR		Study 2005-01 Historical Control N=32
				Defibrotide N=41	Non-defibrotide N=55	
<b>Status at Day + 100 [post-HSCT]</b>						
Alive n(%)	39(38)	33(44)	159(45)	16(39)	17(31)	8(25)
95% CI	29-48	33-55	40-51	24-56	19-45	12-43
Dead	63(62)	42(56)	178(51)	25(61)	38(70)	25
Day + 100 status not available	0	0	14(4)	0	0	N/A

The Day + 100 survival post-HSCT was similar across the studies with range of Day + 100 post-HSCT survival between 38%-45%. The following figure provides a forest plot of survival for all of these studies to include the historical control arm from Study 2005-01.

**Figure 7 Forest plot for 4 studies with Day + 100 survival after transplantation**

Source: FDA Statistical Review by Yuan-Li Shen Ph.D. and Xin Gao Ph.D.



Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

*Reviewer Comment: Across the studies the Day + 100 survival rate was higher compared to the historical control arm of 25% survival at Day+ 100 post HSCT and the non-defibrotide arm (31%) of the CIBMTR registry study.*

*The CIBMTR registry data provides additional supportive information despite being retrospective in nature. When comparing the treatment group in Study 2005-01 to the non-defibrotide group in Study CIBMTR, a numerical survival advantage is demonstrated for the treatment group. Despite the limitations with cross study comparisons, the consistent positive findings in survival for the defibrotide treated arms are compelling. Taking these findings into consideration, there is substantial weight of evidence that defibrotide prolongs survival at Day +100 post-HSCT for patients with hepatic VOD with multi-organ dysfunction.*

A pooled analysis of three studies (Study 2005-01, 99-118, 2006-05) by the treatment indication (severe VOD with MOF who received 6.25 mg/kg every 6 hours) was performed by the Applicant and the confirmed by this reviewer. This pooled analysis is exploratory only as this was not prespecified in the SAP.

**Table 60 Pooled Efficacy Analysis for Study 2005-01, Study 99-118 and 2006-05**

Status, n(%)	HC n-32	Defibrotide 25 mg/kg N=528
<b>Status at Day + 100 post-HSCT</b>		
Alive	8(25)	231(44)
Dead	24(75)	283(54)

*Reviewer Comment: The pooling of the data was conducted by the Applicant and confirmed by the FDA reviewer. The Day + 100 survival post HSCT pooled survival data demonstrates survival advantage. The pooling of the data however was not prespecified in SAP and is exploratory only.*

### 7.1.2. Secondary and Other Endpoints

The key secondary endpoints across the trials included CR rate by Day + 100 post-HSCT. Due to differences in definition for CR across trials, no pooled or side-by-side analysis was performed.

Study 2004 was a phase 3 multicenter, prospective, randomized, open-label controlled study for the prophylactic use of defibrotide for the prevention of VOD in high-risk pediatric patients. The efficacy data demonstrated from this study supports the key supportive trials but cannot be compared side-to-side or in a pooled analysis since indication population different.

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

### 7.1.3. Subpopulations

Subgroup analyses for the intended population (hepatic VOD with MOF post HSCT) in patients who received defibrotide (6.25 mg/kg) were explored. Across all subgroups there was a survival advantage at Day + 100 post HSCT. Differences in subgroups were noted and included the following:

- Day + 100 survival for Ventilator/dialysis dependent patients was 34% compared to 50% for patients who were not ventilator/dialysis dependent.
- Day + 100 survival was 36% for patients with acute leukemia compared to 52% for patients with alternative diagnosis
- Patients who received autologous transplant had better survival at Day + 100 compared to allogeneic transplantation patients (65% vs 42%, respectively).

These differences are not unexpected given the underlying severity of VOD, disease state and type of transplant.

The following table shows the number of pediatric patients enrolled in the 3 studies. In total there were 255 (48%) pediatric patients with the majority between ages 2-11 years.

**Table 61 Pediatric Patients enrolled in the key efficacy trials.**

Age	2005-01 N=102	99-118 N=75	2006-05 N=351	Total N=528
>16 years	58(57)	53(71)	16(46)	273(52)
<16 years	44(43)	22(29)	189(54)	255(48)
0-23 months	17(39)	5(23)	54(29)	76(30)
2-11 years	17(39)	13(59)	94(50)	124(49)
12-16 years	10(23)	4(18)	41(22)	55(22)

#### Pediatric Subgroup Efficacy

Children had better survival outcomes compared to adults and within the pediatric subgroups, younger children (< 11 years of age) trended toward better survival outcomes. However pediatric patients tend to have better outcomes after transplantation.

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

**Table 62 Pediatric Survival at Day + 100 post HSCT across the 3 trials.**

	<b>2005-01 N=102</b>	<b>99-118 N=75</b>	<b>2006-05 N=351</b>	<b>Total Defibrotide(pediatric) N=528</b>
<b>Pediatric(&lt; 16 years)</b>				
<b>Status at Day + 100 post HSCT</b>	44(43)	22(29)	189(54)	255(48)
Alive	22(50)	15(69)	94(50)	131(51)
Dead	22(50)	7(32)	83(44)	112(44)
Not available	0	0	12(6)	12(95)
<b>Adult &gt; 16 years</b>				
<b>Status at Day + 100 post-HSCT</b>	58(57)	53(71)	162(46)	273(52)
Alive	17(29)	18(34)	65(40)	100(37)
Dead	41(71)	35(66)	95(59)	171(63)
Day + 100 status N/A	0	0	2(1)	2(<1)

*Reviewer Comment: Due to confounding factors related to transplantation risk factors, no definitive conclusion can be made that defibrotide works better in pediatric patients than adults..*

#### **7.1.4. Dose and Dose-Response**

An exposure-response analysis was not conducted for defibrotide, because insufficient PK data were collected from patients who took part in the Phase 2 and Phase 3 trials. In the results from the dose-finding Phase 2 study 99-118, where CR rate and Day + 100 survival were compared at two defibrotide dose levels (25 mg/kg/day versus 40 mg/kg/day), no meaningful difference in either CR rate or Day + 100 survival was observed.

#### **7.1.5. Onset, Duration, and Durability of Efficacy Effects**

With respect to duration of dosing, Study 99-118 (phase 2 dose-finding study) recommended a minimum duration of dosing for 14 days. However the actual median length of treatment was 19.5 days in both defibrotide arms (25 mg/kg/day and 40 mg/kg/day). The pivotal study, 2005-01, the recommended dose of defibrotide was to be administered for a minimum of 21 days (25 mg/kg/day). In summary, defibrotide is to be administered for a minimum of 21 days and continued to hepatic VOD has resolved. Given the expected short-term usage of defibrotide, loss of efficacy or tolerance effects are not anticipated.

### **7.2. Additional Efficacy Considerations**

#### **7.2.1. Considerations on Benefit in the Postmarket Setting**

While patient populations enrolled to clinical trials tend to differ in various ways from the

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

broader population of patients, there are no clear signals noted in this review that would suggest differences in responses

### 7.3. Integrated Assessment of Effectiveness

The efficacy of defibrotide sodium was evaluated by Day + 100 survival after transplantation. This endpoint is the most meaningful endpoint for patients with severe VOD. Temporally, VOD occurs prior to Day + 100 post-HSCT and most often occurs within the first 30 days post-HSCT. Although survival at later dates (Day + 180) or overall survival represent a clinically meaningful outcome to patients. The temporal occurrence of VOD makes survival at Day + 100 survival the endpoint that most accurately captures the efficacy of defibrotide.

The pivotal study, 2005-01, demonstrated a Day + 100 survival after transplantation in 25 patients [38% (95% CI: 29, 48)] in the defibrotide arm versus 8 patients [25% (95% CI: 12, 43)] in the historical control arm. The totality of evidence from the following three trials demonstrates a similar survival benefit for defibrotide in the treatment of hepatic VOD with end-organ dysfunction:

- Study 99-118: Survival at Day + 100 post-HSCT was 44% (95% CI: 40,51) in the 25 mg/kg/day group.
- Study 2006: For the indication population (severe VOD with MOF post –HSCT) the Day +100 survival post-HSCT was 47% (95% CI: 40, 51).
- Study CIBMTR (Registry Data): The Day + 100 survival rate post-HSCT for the defibrotide group was 39% (95% CI: 24, 56) versus 31% (95% CI: 19,45) for the non-defibrotide arm (best supportive care).

The Day + 100 survival demonstrated in these four studies is higher than the historical control arm from Study 2005-01 and the supportive care arm from the CIBTMR registry data study.

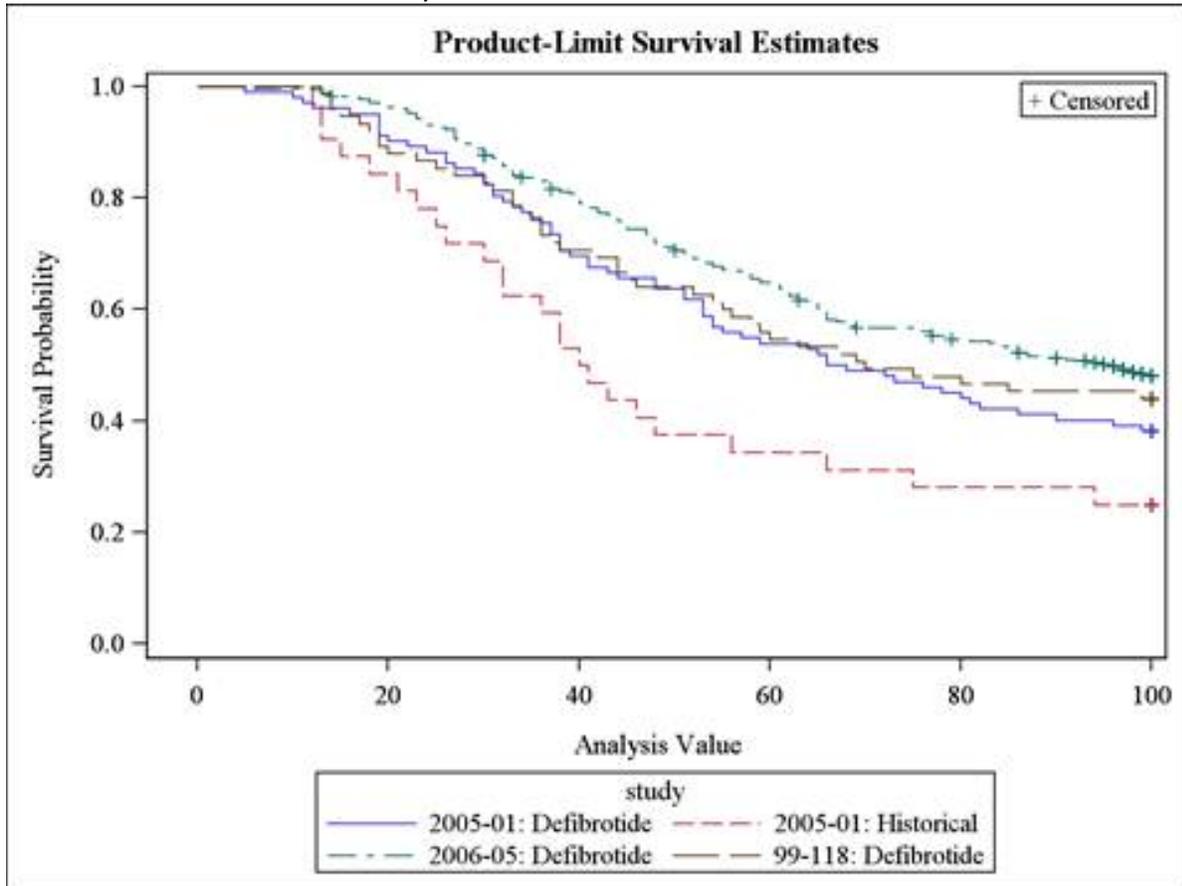
The prevention study (Study 2004) while not convincing enough for an indication in the prevention of VOD does provide a signal and supports the premise that defibrotide can reduce the mortality for patients who are at high risk for the development of VOD.

The consistency of the improvement in survival is depicted in the figure below which displays the survival curves for the historical control trial (2005-01), Study 2006-05 and Study 99-118 compared to the historical control arm from Study 2005-01.

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

**Figure 8 Time-to-Event Survival Analysis for Study 2005-01, Study 99-118 and Study 2006-05**

Source: FDA Statistical Review by Xin Gao Ph.D. and Yuan-Li Shen Ph.D.



It is the opinion of this reviewer that the benefit risk balance of defibrotide is positive for the treatment of hepatic VOD with end-organ dysfunction based upon the weight of the evidence from all four studies. To further explain how this conclusion was reached additional discussion is warranted regarding Study 2005-01(historical control trial). Five issues arose during the review of this NDA with regard to the efficacy evaluation in Study 2005-01: 1) Use of a Historical Control Study 2) Source of Historical Control Subjects 3) Validity of the Selected Historical Control 4) Lack of control for multiplicity (unplanned interim analyses), and 5) Lack of details for prespecified analysis plan and statistical robustness of treatment effect.

#### Issue 1: Use of a Historical Control Study

Historical control designs are generally reserved for special circumstances since the historical control populations may not be as well assessed to pertinent variables as concurrent control

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

populations. The special circumstances include diseases with a high predictable mortality when too few patients are available to conduct a randomized trial. The use of a randomized concurrently controlled design is not ethically feasible in patients with hepatic VOD with multi-organ dysfunction. Hepatic VOD with multi-organ dysfunction has a high predictable mortality (> 80%) with no available therapeutic options and unquestionably meets a special circumstance.

#### Issue 2: Source of the Historical Control Subjects

This reviewer recognizes that the selection of the historical control group occurred concurrently with the selection of the defibrotide group. Due to the mortality of the disease and no available treatment options, there are no prospective trials with sufficient similar populations to be used as a historical control group. While there is registry data, the individual patient data is not available and thus the use of registry data while supportive could not be used as the historical control. In summary, the only available method to obtain the historical control group was selection from the same transplantation centers as the treatment group. The inclusion in the historical control group spanned from 1995-2007 with the majority of patients (66%) recruited during 2000-2006. Recruitment into the defibrotide arm occurred from 2006-2008. The overlap mostly occurred over 1-2 years thus minimizing the concern of concurrent enrollment. The selection of the HC from the same transplantation centers during same time frame as treatment group while not ideal represents the best available method in this disease setting.

Temporal bias can also be a concern in the conduct of the study. The patients in the historical control arm were recruited from 1995 to 2007, with majority of patients recruited between 2000 and 2006. Most of the treatment group was recruited during 2000 to 2006. This difference in time frame could introduce temporal bias however despite improvements in supportive care for patients undergoing transplantation during this time span, the mortality for patients with severe VOD with MOF has not improved (> 80%)(Coppell 2010); therefore temporal bias is not as relevant.

#### Issue 3: Integrity of the Historical Control Selection Process

This reviewer recognizes that a placebo-controlled trial is not ethically feasible in a population of patients with severe VOD with MOF due to high mortality for patients and lack of approved treatment for this indication; therefore the validity and selection process of the historical control arm is vital to the integrity of the trial. The issue is that clinical outcomes were analyzed during the selection process and triggered rereview and elimination of some of the historical patients.

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

The amendments to the MRC SOP that resulted due to the 2<sup>nd</sup> DSMB meeting allowing additional data query from charts after chart partition dates actually enabled better screening of the historical charts to more closely resemble screening of patients in the defibrotide arm by study Investigators

The diagnosis of VOD is complex and occurs in a continuum. The additional interim analyses of both the historical control arm and treatment arm were performed at the request of the DSMB to ensure adequate quality of data and as part of the remediation effort. A review of the narratives by this reviewer for the 54 patients excluded from the final MRC review concluded that an alternate etiology for symptomology could be explained. Thus, the enrollment of these 54 patients into the final control group would not have represented the appropriate population for this trial.

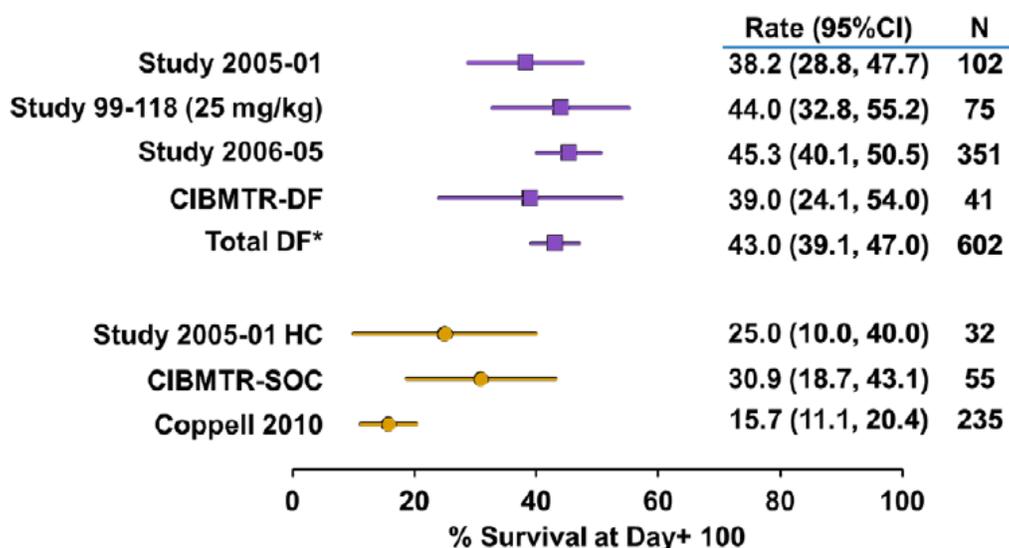
These unplanned analyses helped to mitigate potential issues regarding the comparability of the historical control and the treatment group. Although the final recommendation of the DSMB was to enroll at least 80 patients in the Historical Control group, the Agency and Applicant agreed that adding additional centers would not be acceptable and could potentially reduce the level of contemporaneousness to an unacceptable level. The unplanned analysis and adaptations helped reduce potential selection bias issues and ultimately, the selection of the historical control group remains valid. It is the opinion of this reviewer that the blinding of the MRC and rigorous review process provided assurance that the selection of the historical control arm remained unbiased despite the small sample size(n=32).

Additional support for the small sample size comes from the CIBMTR registry data using similar selected parameters as in the historical control arm of trial 2005-01. In the CIBMTR registry study, 8341 HSCT patients were screened for the incidence of severe VOD and was ultimately diagnosed in 1.2% of the screened patients. This is similar to the incidence of severe VOD with MOF in the historical control arm (1.5%) with screening of 6867 patient charts. The similarity in incidences of hepatic VOD with MOF in two different trials lends further support to the final size of the historical control. In summary, the historical control group, although small, was selected appropriately and is acceptable as the comparator arm in this clinical setting.

The validity of the historical control arm in study 2005-01 can further be supported by similar survival rates in the historical control, standard of care arm in the CIBMTR registry study and from literature. The following forest plot was constructed by the Applicant and also includes the expected mortality for patients with VOD with MOF from the literature (Coppell et al 2010).

**Figure 9 Survival at Day + 100/Proportion Alive and 95% Confidence Intervals**

Source: Applicants Response to Information Request December 9, 2015. Module 1.11.4 Page 21/53



\* Data from CIBMTR registry omitted due to possible duplicate patients in 2006-05

- Total DF includes the 74 patients on Study 99-118 who received 40 mg/kg defibrotide

The historical control survival rates are comparable to the standard of care arm in the CIBMTR registry and actually higher than literature reports. This lends further credence to the validity of the historical control arm of Study 2005-01. A comparison of the standard-of-care arm from the CIBMTR registry (31%) to the treatment arm in study 2005-01 (38%) demonstrates an observed survival difference of 7% difference. For a disease that has mortality of greater than 80% with no therapeutic options, an improvement of 7% is clinically meaningful.

In summary, the review process by the MRC ensured that the selection of the historical control group was stringent and that only patients with hepatic VOD with end-organ dysfunction were included. The survival in the historical control (75%) is slightly lower than what would be expected based on literature (> 80%, Coppell 2010) and the CIBMTR registry (79%). All the evidence indicates that the historical control group and the treatment group were well balanced and comparable.

**Issue 4: Lack of Adjustment for Multiplicity**

There was no prespecified alpha control for the multiple unplanned adaptations during the conduct of the trial. The additional interim analyses of both the historical control arm and

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

treatment arm were performed at the request of the DSMB to ensure adequate quality of data and as part of the remediation effort. The statistical concerns regarding the multiplicity are less concerning given the endpoint of overall survival as survival endpoints are much less subject to bias than response endpoints. The consistency of the survival benefit and totality of evidence for defibrotide in patients with hepatic VOD with end-organ dysfunction provide sufficient supportive evidence for an improvement in mortality.

#### Issue 5: Analysis Plan not Sufficiently Prespecified

The estimated difference in survival calculated by the Applicant using the propensity-stratified and weighted estimate is 23% with 95% CI (5%, 41%) with a p-value of (b) (4) by the Koch method. The propensity-stratified estimated difference was prespecified in the SAP, and the FDA statistical review team was able to verify this estimated difference of 23%. However, the algorithms and ranking methods used for the derivations of the propensity score were not prespecified.

The Applicant and FDA Statistical Review team both performed additional analyses for the propensity estimated difference in survival. The additional analysis performed by the FDA Statistical review team varies by which propensity score strata are used with estimated differences ranging from 13% to 23% with p-values ranging from (b) (4). Sensitivity analyses conducted by the Applicant to ensure that the SAP stipulation, for the scenario in which there were less than 2 patients in the a quintile was met, demonstrated estimated survival differences between 18%- 23% with p-values in the range of (b) (4).

This clinical reviewer acknowledges difficulty in interpretation of the magnitude of the treatment effect depending upon which strata and algorithm used. The totality and consistency of an improvement in the mortality with the use of defibrotide provides enough weight of evidence to support approval of defibrotide sodium for the treatment of patients with hepatic VOD with end-organ dysfunction.

In summary, the high mortality rate for patients with hepatic VOD with end-organ dysfunction and no available therapy in conjunction with the weight of the totality of evidence across all four studies supports a recommendation for approval of defibrotide sodium. It is this reviewer's opinion that the benefit of defibrotide is positive for the treatment of hepatic VOD with end-organ dysfunction based upon the following conclusions:

- Hepatic VOD with multi-organ dysfunction has a high predictable mortality (> 80%) with no available therapeutic options and meets a special circumstance for the use of a historical controlled trial.

## Clinical Review

Tanya Wroblewski, M.D.

Donna Przepiorka, M.D. Ph.D.

NDA 208114

Defitelio (Defibrotide Sodium)

- The selection of the historical control concurrently with the defibrotide group was the only option given the paucity of sufficient randomized control trials with similar populations and lack of subject level registry data.
- All evidence indicates that the historical control and treatment group were well balanced and comparable.
- The survival rates from Study 99-118, Study 2006-05, and the CIBMTR registry study reinforce that defibrotide reduces the mortality rate in patients with severe hepatic VOD with end-organ dysfunction.

In summary, the totality of survival data from study 2005-01 supported by the survival data from Study 99-118, expanded access IND study (2006-05), and registry data from CIBMTR support the recommendation of regular approval of the marketing application for defibrotide sodium at a recommended dose of 6.25 mg every 6 hours for up to 21 days or until resolution of hepatic VOD for the treatment of patients with severe VOD (b) (4)

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

## 8 Review of Safety

---

### Safety Review Approach

#### 8.1.1. Clinical Studies/Trials Used to Evaluate Safety

The following studies were included in the defibrotide clinical development program and considered in detail for the clinical review of safety for this NDA:

- There were six studies or clinical trials in patients. These included the hepatic VOD treatment trials 2005-01 and 99-118, the hepatic VOD prophylaxis trial 2004, the CIBMTR registry study, and the compassionate use experience in DF-CUP and 2006-05. The designs of these studies were described in Section 5.1.
- There were two PK/PD studies in healthy volunteers or volunteers with renal insufficiency. These included R09-1425 and 2012-03-PKREN. These studies are described in Section 5.1.

The sponsor also submitted reports for five PK/PD studies in healthy volunteers or volunteers with cancer or peripheral vascular disease. These studies were conducted with pre-1995 product (see Section 8.1.3) and are considered separately where relevant.

Lastly, the sponsor provided an independent Clinical Study Report for the DF-VOD Trial, which they described as an investigator-initiated study (Module 5.3.5.3 Integrated Summary of Safety page 25). Since no data set was submitted for review to confirm the results reported, the safety information from this trial will be discussed separately in Section 8.9.2.

#### 8.1.2. Anticipated Safety Issues

Potential class safety issues might result from either the chemical class or the pharmacologic effect of a drug. Defibrotide is an oligonucleotide mixture. There are two FDA-approved oligonucleotides. Mipomersen (Kynamro) is a 20-mer oligonucleotide approved for treatment of homozygous familial hypercholesterolemia. It binds to and disrupts the function of apolipoprotein B mRNA. Labeling carries a warning about potential hepatotoxicity. It also causes flu-like symptoms and thrombocytopenia, and it is immunogenic. Pegaptanib (Macugen) is a 28-mer oligonucleotide conjugated to polyethyleneglycol (PEG) approved for treatment of neovascular age-related macular degeneration. It binds to and inhibits vascular endothelial growth factor. As it is administered by local injection, the majority of the adverse reactions to Pegaptanib are intraocular events, but labeling also carries a warning for anaphylaxis. The only unifying safety issues in this class are the potential for immunogenicity and hypersensitivity reactions.

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

Pharmacologically, defibrotide has been shown to enhance the enzymatic activity of plasmin to hydrolyze fibrin clots in vitro, and to increase t-PA and thrombomodulin expression while decreasing vWF and PAI-1 expression in microvascular endothelial cells in vitro. There are multiple FDA-approved thrombolytic drugs that enhance the activity of plasmin. These drugs carry warnings for bleeding, increased bleeding with concomitant use of anticoagulants or antiplatelet agents, and interference in coagulation tests in vitro. All of these can be considered expected safety issues for defibrotide based on its pharmacological effects.

### 8.1.3. Safety Issues from Other Disciplines

The Biopharmaceutics reviewer noted that defibrotide drug substance (b) (4) (b) (4) for the purposes of this safety review, such product will be referred to (b) (4) but thereafter, all drug substance used only tissues of porcine origin. Additionally, all drug product as of 2009 was (b) (4). Since there is no means by which to determine if the original product manufactured (b) (4) would have the same safety profile as the current product using only drug substance of porcine origin, this safety review will be focused (except where noted) on studies conducted only with drug substance identified by the sponsor as manufactured (b) (4).

The Drug Product reviewers noted that the strength of defibrotide as described in the protocol was based on the salt form of the drug. (b) (4)

(b) (4) For the purposes of this safety review, the term defibrotide denotes defibrotide sodium, and the dose will be displayed as reported in the protocols using the strength based on the salt. The dosing recommendation for labeling is discussed in Section (b) (4).

The Nonclinical Pharmacology/Toxicology reviewer noted that in the 13-week toxicity studies in rats and dogs, defibrotide transiently prolonged the aPTT in rats and in dogs, and the PT in rats. These findings were observed at doses at least 6 times higher than the proposed clinical dose. It is not clear whether these were direct in vivo effects or were related to interference with the coagulation assays in vitro. The coagulation tests in the clinical trials will receive close scrutiny in this safety review.

### 8.1.4. Review Strategy

A total of 1894 individuals were exposed to defibrotide in the sponsored clinical studies. Table 63 shows the numbers of individuals who received defibrotide by protocol, dose and diagnosis. Protocols 2005-01 and 2004 were randomized trials that included control subjects not treated with defibrotide. Safety data were included for 32 control subjects on Protocol 2005-01 and for 176 control subjects from the prophylaxis period on Protocol 2004. There were an additional

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

41 defibrotide-treated patients with severe hepatic VOD and 55 untreated controls in the registry study CIBMTR for whom very limited safety data were available.

**Table 63: Numbers of Patients/Subjects Exposed to Defibrotide**

Protocol	Total Daily Defibrotide Dose	Number Treated	Diagnosis			HSCT VOD with MOF 25 mg/kg
			HSCT VOD with MOF	Other VOD	Other <sup>a</sup>	
<i>Studies with Patients</i>						
2005-01	25 mg/kg	102	102	0	0	102
99-118	25 mg/kg	74	74	0	0	74
	40 mg/kg	75	75	0	0	0
2006-05	25 mg/kg	649	353	296	0	353
DF-CUP	10 mg/kg	85	37	48	0	0
	25 mg/kg	272	98	174	0	98
	40 mg/kg	226	59	167	0	0
	60 mg/kg	46	23	23	0	0
	80 mg/kg	9	4	5	0	0
	Unknown	72	32	40	0	0
2004	25 mg/kg	214	57	3	154	57
<i>Studies with Volunteers</i>						
R09-1425	Up to 15 mg/kg	52	0	0	52	0
2012-03-PKREN	25 mg/kg	12	0	0	12	0
	6.25 mg/kg	6	0	0	6	0

Source: FDA analysis

<sup>a</sup>Includes patients who received defibrotide solely for VOD prophylaxis or for treatment of other disorders, and healthy volunteers or volunteers with renal dysfunction on PK/PD studies.

There were no controlled trials that had adequate data for comparative analyses across all safety parameters for the intended population. Study 2005-01 was the only controlled trial in the intended population, but because the methodology used to collect adverse event (AE) data for the historical controls differed from that used in the treatment group (see Section 8.3.1 and 8.3.2), it was concluded that direct comparisons of treatment-related adverse events (TEAE) between these groups were not appropriate. Therefore, the objective of the safety review was to develop the safety profile descriptively for the intended population.

Overall, there were 684 subjects with hepatic VOD and MOF after HSCT who were treated with defibrotide 25 mg/kg/day in five protocols (Table 63 Column 7). The population of interest for the assessment of adverse events was limited to subjects on Studies 2005-01 and 99-118 treated with the proposed dose. This is referred to as the Selected Safety Population (SSP):

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

**Selected Safety Population (SSP):** 176 subjects with hepatic VOD and MOF after HSCT who were treated with defibrotide 25 mg/kg/day on Studies 2005-01 and 99-118

The expanded access / compassionate use protocols (2006-5 and DF-CUP) had no monitoring or source data verification, and a proportion of the population treated on Study 2004 had received defibrotide prophylaxis, so subjects from these studies were excluded from the SSP. Where available, data were also summarized descriptively by FDA by grouping the subjects not in the SSP as follows:

**Other Defibrotide-Treated Patients:** 1648 patients not in the SSP but who were treated with various doses of defibrotide for prevention of VOD or for the treatment of VOD or other disorders

**PK/PD Study Volunteers:** 70 healthy subjects or subjects with renal insufficiency who participated in defibrotide the PK/PD studies R09-1425 and 2012-03-PKREN

Objective data, such as laboratory tests, vital signs and ECGs, were considered less susceptible to bias, so credence was given to comparisons between study arms or groups for such data when available.

Although the major focus of the review was the clinical trial data for the SSP, FDA considered all available safety information for defibrotide, including where applicable safety results in the volunteers from the PK/PD studies, published information on individuals in the VOD and non-VOD populations treated with defibrotide, legacy studies (b) (4), and the postmarketing safety data for all formulations of defibrotide.

This safety review used the data sets submitted in the original application received 7/31/2015. The ISS data set specifically was used for pooled analyses. The categorization of adverse events is described in Section 8.3.2 below. In contrast to the post hoc approach used by the applicant for the analysis of the adverse events of special interest (AESI) hemorrhages and hypersensitivity, FDA utilized terms in the narrow SMQs as noted in Sections 8.5.1 and 8.5.3. Statistical analyses by the safety reviewer were performed using JMP 11.0 (SAS Institute, Inc., Cary, NC). MedDRA Adverse Events Diagnostic (MAED) v1.2 (b) (4) (b) (4) and Empirica Signal (b) (4) were used to assess for safety signals. Unless stated otherwise, all p-values are unadjusted for multiplicity and should be interpreted with caution.

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

## 8.2. Review of the Safety Database

### Characteristics of the Safety Population

Table 64 shows the demographics and baseline characteristics of the three populations assessed in the safety analyses. Forty percent of the subjects in the SSP was  $\leq 18$  years old, 89% were allogeneic transplant recipients, 43% had been transplanted for leukemia, 18% were ventilator-dependent, and 13% were dialysis-dependent. The demographics and characteristics of the patients in Study CIBMTR were described in Tables 43-44 in Section 6.3.

**Table 64: Safety Population – Demographics**

	SSP (n=176)		Other Defibrotide- Treated Patients (n=1648)		PK/PD Study Volunteers (n=70)	
<u>Age</u>						
Median	25 yrs		14 yrs		24 yrs	
(range)	(0.1 – 72 yrs)		(0.1 – 70 yrs)		(19-76 yrs)	
<u>Age Group</u>						
<17 yrs	65	37%	899	55%	0	0
17 to <65 yrs	110	63%	729	44%	61	87%
$\geq 65$ yrs	1	1%	20	1%	9	13%
<u>Gender</u>						
Male	105	60%	970	59%	49	70%
Female	71	40%	678	41%	21	30%
<u>Race/Ethnicity</u>						
White	137	78%	480	29%	49	70%
Hispanic	14	8%	104	6%	-	-
Other	7	4%	52	3%	7	7%
Black	12	7%	46	3%	11	16%
Asian	6	3%	40	2%	5	7%
Unknown	0	0%	926	56%	0	0
<u>Reason for Defibrotide</u>						
VOD with MOF after HSCT	176	100%	738	45%	0	0
Other VOD	0	0%	756	46%	0	0
Other (Including prophylaxis)	0	0%	154	9%	0	0
PK/PD Study	0	0%	0	0%	70	100%
<u>Dialysis or Ventilator Dependent</u>						
No	134	76%	1403	85%	70	100%
Yes	42	24%	245	15%	0	0

Source: FDA analysis

### 8.2.2. Exposure

Due to limitations in the information available about dosing (see Section 8.3.1), a detailed assessment of exposure was limited to the SSP. Table 65 shows the extent of defibrotide

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

exposure for the SSP. Approximately half of the subject in the SSP were treated for 21 days or less, and 99% received 60 days or less of treatment with defibrotide.

**Table 65: SSP - Exposure**

<b>Defibrotide Treatment</b>	<b>SSP (n=176)</b>
Median average daily dose (range)	23.5 mg/kg/day (5 - 36.5 mg/kg/day)
Median total dose (range)	500 mg (13 – 2021 mg)
Median duration of dosing (range)	21 days (1 – 83 days)
Duration of dosing	
≤21 days	92 (52%)
22-60 days	82 (47%)
>60 days	2 (1%)

Source: FDA analysis using summary data only

### 8.2.3. Adequacy of the Safety Database

According to the Center for International Blood and Marrow Transplantation, the age distribution for all patients with severe VOD transplanted in the US 2008-2014 was 46% for those ≤18 years old, 49% 19-64 years old, and 5% ≥65 years old (Response to Information Request received 11/20/2015), so the age distribution in the SSP is comparable to the intended population. There are no reports of gender or race/ethnicity distribution in patients with VOD, but the distribution in Table 64 is consistent with the gender and race/ethnicity of patients undergoing HSCT in general. As such, the safety database is essentially representative of the target population by demographic factors.

Of note, Studies 2005-01 and 99-118 both excluded patients with on-going clinically significant bleeding, patients being treated for hypotension with 2 or more vasopressors, patients with grades B-D acute GVHD (except grade B skin alone), or those who required concurrent use of medications that increased the risk of hemorrhage. In addition, as shown in Table 65, nearly all subjects in the SSP received ≤ 60 days of dosing with defibrotide.

***Reviewer Comment: Due to the exclusion criteria of the protocols, the results of the safety analysis may not reflect some of the most medically complex patients who develop VOD. This should be clarified in the Prescribing Information. Additionally, since most subjects in the SSP received only up to 60 days of treatment, the safety of longer-term use is unknown. As such, the current available data do not support the conclusion of safety for the applicant's proposal***

(b) (4)

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

### 8.3. Adequacy of Applicant’s Clinical Safety Assessments

#### 8.3.1. Issues Regarding Data Integrity and Submission Quality

With regard to data integrity, the safety reviewer noted that the protocols were inconsistent with regard to adverse event recording instructions to the investigators. Table 66 describes the adverse event recording instructions by protocol. None of the protocols for treatment or prophylaxis of hepatic VOD required recorded all adverse events.

**Table 66: Instructions to Investigators for Recording Adverse Events**

Protocol	Deaths Recorded	SAEs Recorded	Adverse Events Recorded	Source <sup>a</sup>
<i>Studies with Patients</i>				
2005-01 Patients	Yes	Excluded symptoms of VOD	Excluded the expected complications of HSCT and the signs and symptoms of the original disease or the target disorder unless considered serious.	Protocol Section 9.2.1
Controls	Yes	No	Excluded the expected complications of HSCT and the signs and symptoms of the target disorder	Clinical Study Report Section 9.5.1.2
99-118	Yes	Yes	Included unanticipated events of any grade and grade 4-5 expected events	Protocol Sections 5.8 and 6.1
2006-05	Yes	Yes	Excluded the expected complications of HSCT and the signs and symptoms of the original disease or the target disorder unless considered serious.	Protocol Section 7.0
2004	Yes	Yes	Included only events considered drug-related	Protocol Sections 4.4 and 4.5
DF-CUP	Voluntary	Voluntary	Voluntary	Statistical Analysis Plan 2.0
CIBMTR	Yes	No	No	Clinical Study Report Section 9.5.3
<i>Studies with Volunteers</i>				
R09-1425	Yes	Yes	Yes	Protocol Section 13.2
2012-03-PKREN	Yes	Yes	Yes	Protocol Section 9.2

Source: FDA analysis

<sup>a</sup>Documented instructions to investigators.

FDA also considered information provided by the investigators regarding ascertainment of adverse events. As described in Section 4.1, the inspection of Study 2005-01 Site 11 revealed critical protocol violations, including late reporting of SAEs. In a letter dated 11/16/2015 from (b) (4) responding to the Form FDA 483 Observations at Site 11, he indicated:

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

(b) (4)

In a Response to an Information Request received 11/6/2015:

- The applicant acknowledged that the assessment of seriousness was “subject to medical judgment and can limit the assessment of SAEs in any open-label trial design.”
- The applicant indicated that the “incompleteness of non-serious AE reporting could potentially lead to an underestimation of the risk that defibrotide therapy may increase the incidence of well-known complications of HSCT or aggravate the underlying symptoms of VOD with MOD.”
- The applicant maintained that “Even if an excluded event occurred with much higher frequency in the treatment group, the risk/benefit impact of that non-serious event would be minimal in the setting of a life-threatening illness; safety conclusions based on SAEs, including those that led to death, would be expected to have greater clinical relevance.”
- The applicant’s position was that “the omission of non-serious adverse events associated with HSCT, VOD, or organ dysfunction does not have a clinically meaningful impact on the safety profile or risk/benefit assessments for defibrotide in the treatment of VOD with MOD following HSCT.”
- The applicant concluded that “the safety data provided in the NDA accurately reflect the safety profile of defibrotide in this patient population.”

***Reviewer Comment: It is clear that there is abundant potential for bias in the selection of adverse events recorded and in the the identification of SAEs in defibrotide clinical trials. As such there is a high risk that the safety profile is incomplete or inaccurate. A more objective approach, such as recording all grades 3-5 AEs and all SAEs as defined in the CFR independent of attribution, would have provided a less biased data file. How this affects the conclusions of the assessment of safety data is discussed in Section 8.10.***

With regard to the submission, the safety reviewer noted a number of issues:

- In the ISS data file adex.xpt, the units of dosing were not standardized across protocols, so the derived variables for exposure could not be confirmed.

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

- In the ISS data file admh, controlled text was not used for the medical history terms, so the effect of pre-existing comorbidities on safety outcomes could not be assessed.
- In the ISS data file adae.xpt, there were internal inconsistencies between variables describing action, outcome and relatedness for TEAEs. The subsections in this review identify which variables were used by the safety reviewer for the analyses of TEAEs.
- The ISS data files for laboratory tests did not include the CTCAE grade.
- In pdf documents, bookmarks were generally displaced by 1-2 pages from the target.

### 8.3.2. Categorization of Adverse Events

In the ISS data set, AEs were reported down to the verbatim term and coded using MedDRA 16.0. In general, AEs that started or worsened in severity after the date the patient received the first dose of defibrotide through 30 days after the last dose was considered a TEAE by the applicant. If the timing of an AE could not be identified because of missing data, then the AE was assumed to be a TEAE. The investigator was to assign seriousness, severity and relatedness. The system used to grade TEAEs or laboratory abnormalities was not standardized across protocols. Relatedness, severity, seriousness, outcome and study drug action were not recorded for TEAEs in the historical controls on 2005-01.

The applicant identified two AESI: hemorrhage and hypotension. The terms used for these two AESI were identified post hoc by the applicant from the reported Preferred Terms in the clinical studies (Module 5.3.5.3 Integrated Summary of Safety Sections 4.6.2 and 4.6.3).

Acute GVHD and hypersensitivity were two additional significant adverse events evaluated by the applicant. Acute GVHD was identified by the Preferred Term and date of onset. Hypersensitivity was identified by post hoc search of the reported Preferred Terms.

For the purposes of development of the safety profile, the applicant utilized two pooled populations:

**Pool A:** Studies 2005-01 (including historical controls) and 99-118

**Pool B:** Studies 2005-01, 99-118 and 2006-05

Due to the limited safety information recorded for 2006-05, only deaths and SAEs were evaluated by the applicant for Pool B.

### 8.3.3. Routine Clinical Tests

The schedule of safety assessments varied somewhat between 2005-01 and 99-118 (see Section 6 for a detailed description). In general, common laboratory tests were required daily until cessation of therapy or discharge. On 2005-01, additional testing was required at Day +100 and Day +180 after HSCT, but there was no specific testing required after cessation of therapy on 99-118.

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

**Reviewer Comment: The schedules described are adequate for assessing safety while on therapy, but delayed effects or peak effects may have been missed due to lack of follow-up testing in the immediate posttreatment period.**

## 8.4. Safety Results

### Deaths

Table 67 shows the numbers of deaths reported in the safety population. Over half of the subjects in the SSP died within 30 days of the last dose of defibrotide. The SOC with the highest incidence of fatal events were General disorders and Hepatobiliary disorders. Excluding the Preferred Term veno-occlusive disease, the incidence of fatal adverse events in the SOC Hepatobiliary disease was only 3%. Within the SSP, the most common fatal adverse events were multi-organ failure (22%), respiratory failure (7%), pulmonary alveolar hemorrhage (4%), sepsis (4%), graft versus host disease (3%), renal failure (3%), pneumonia (2%), hepatic failure (2%) and hypoxia (2%).

**Table 67: Safety Population - Deaths**

	SSP (n=176)		Other Defibrotide- Treated Patients (n=1648)		PK/PD Study Volunteers (n=70)	
<u>Deaths</u>						
Deaths due to any cause	128	73%	740	45%	0	0
Deaths within 30 days of last dose	97	55%	583	35%	0	0
<u>Fatal adverse events by SOC</u>						
General disorders and administration site conditions	39	22%	127	8%	0	0
Hepatobiliary disorders	36	20%	105	6%	0	0
Respiratory, thoracic and mediastinal disorders	25	14%	85	5%	0	0
Infections and infestations	21	12%	81	5%	0	0
Renal and urinary disorders	7	4%	26	2%	0	0
Immune system disorders	6	3%	22	1%	0	0
Nervous system disorders	6	3%	18	1%	0	0
Neoplasms benign, malignant and unspecified	5	3%	17	1%	0	0
Vascular disorders	3	2%	26	2%	0	0
Cardiac disorders	1	1%	27	2%	0	0
Gastrointestinal disorders	1	1%	14	1%	0	0
Blood and lymphatic system disorders	1	1%	11	1%	0	0
Injury, poisoning and procedural complications	1	1%	7	<1%	0	0
Congenital, familial and genetic disorders	1	1%	0	0	0	0
Metabolism and nutrition disorders	0	0	9	1%	0	0
Investigations	0	0	3	<1%	0	0
Musculoskeletal and connective tissue disorders	0	0	2	<1%	0	0
Psychiatric disorders	0	0	4	<1%	0	0

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

**Table 67: Safety Population - Deaths**

	SSP (n=176)		Other Defibrotide- Treated Patients (n=1648)		PK/PD Study Volunteers (n=70)	
Reproductive system and breast disorders	0	0	1	<1%	0	0
Skin and subcutaneous tissue disorders	0	0	4	<1%	0	0
Surgical and medical procedures	0	0	2	<1%	0	0

Source: FDA analysis

The sponsor noted that for Study 2005-01, there was a numerically lower incidence of fatal TEAE in the treatment arm than in the control group (64% vs 69%), but fatal hemorrhages were more frequent in the treatment arm (15% vs 6%). However, due to the differences in the methodology for capturing TEAE in the two arms of the study, it was not clear that the data on fatal TEAE were accurate.

As a potentially less-biased alternative, FDA assessed a comparison of cause of death rather than fatal TEAE. The causes of death in Study 2005-01 and in the Study CIBMTR as provided by the applicant are listed in Table 68. Although it appears that death due to progression of VOD/MOF was substantially lower in the treatment arm in 2005-01, when all causes of death due to organ failure are grouped, the difference between groups in incidence of death with organ failure is small (44% vs 47%). There was insufficient information collected prospectively on the occurrence of hemorrhage in the patients with progression of VOD/MOF to allow a comparison of death with hemorrhage.

**Table 68: Causes of Death as Report by the Applicant**

Cause of Death	Defibrotide-Treated		Control Group	
<b>Study 2005-001</b>	<b>(n=102)</b>		<b>(n=32)</b>	
Progression of VOD/MOF	33	32%	13	41%
Infection	12	12%	6	19%
Malignant disease	5	5%	1	3%
Graft versus host disease	2	2%	1	3%
Pulmonary hemorrhage	2	2%	0	0%
Acute respiratory distress syndrome	1	1%	1	3%
Acute respiratory failure	1	1%	0	0%
Chronic liver disease	1	1%	0	0%
Defibrotide toxicity	1	1%	0	0%
Diffuse alveolar hemorrhage	1	1%	0	0%
Hemorrhage	1	1%	0	0%
Hepato-renal failure	1	1%	0	0%
Intracranial hemorrhage	1	1%	0	0%
MOF; subarachnoid hemorrhage	1	1%	0	0%
Progressive Tay-Sachs	1	1%	0	0%

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

**Table 68: Causes of Death as Report by the Applicant**

<b>Cause of Death</b>	<b>Defibrotide-Treated</b>		<b>Control Group</b>	
Pulmonary hemorrhage and diffuse alveolar damage	1	1%	0	0%
Respiratory failure	1	1%	0	0%
Respiratory failure secondary to ARDS	1	1%	0	0%
SCT for severe combined immunodeficiency	1	1%	0	0%
Respiratory failure secondary to pulmonary hemorrhage	1	1%	0	0%
Fulminant liver failure	0	0%	1	3%
Myocardial failure secondary to tamponade	0	0%	1	3%
<hr/>				
<b>Study CIBMTR</b>	<b>(n=41)</b>		<b>(n=55)</b>	
Graft Failure	8	20%	13	24%
Infection	8	20%	13	24%
GVHD	4	10%	11	20%
Primary Disease	4	10%	1	2%
VOD	1	2%	0	0%

Source: FDA analysis

There was one cause of death listed specifically as “defibrotide toxicity.” Subject 35D06 was a six year-old boy who was treated with defibrotide 6.25 mg/kg every 6 hours on 2005-01 for VOD. At the start of treatment, he had renal and pulmonary dysfunction, and he was on a ventilator. The treatment course was marked by ecchymoses, petechiae and post-procedural bleeding, all of which resolved. Defibrotide was held only for the post-procedural bleeding. The subject was extubated on study day 16, and defibrotide was discontinued on study day 21. Four days later the subject was reintubated for hypoxia and respiratory distress following a platelet transfusion. During the posttreatment period, the subject had pulmonary bleeding shown by bronchoalveolar lavage (study day 25), epistaxis (study day 31), and a new cerebral hemorrhage on MRI (on study day 31 in comparison to study day 23). Platelets ranged from 19 to 78 Gi/L. The aPTT and INR were elevated during treatment with defibrotide but only slightly so after discontinuation of defibrotide. Blood cultures were positive for coagulase negative staphylococcus, and bronchoalveolar lavage fluid had herpesvirus 6 DNA. The subject expired on study day 36 with progressing hypoxia despite ventilation. There was no postmortem examination. The applicant concluded that despite the onset of severe bleeding events well past 5 half-lives of defibrotide and the evidence for alternative causes of bleeding, defibrotide could not be excluded as the cause of death.

**Reviewer Comments:**

- ***I disagree with the conclusion of the applicant regarding the cause of death for Subject 35D06. There is far greater biological plausibility that the event was caused by infection rather than by defibrotide.***
- ***In aggregate, there was no unusual rate for any reported specific cause of death in the defibrotide-treated subjects, and there was no evidence that defibrotide caused fatal***

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

**events. However, the high background mortality rate and the lack of a standardized approach to determining the root cause of death limits the interpretability of the aggregate data.**

#### 8.4.2. Serious Adverse Events

For Pool A, the applicant reported that the most frequent (>3%) SAEs in subjects treated with defibrotide 25 mg/kg/day included multi-organ failure (22%), veno-occlusive liver disease (18%), hypotension (11%), respiratory failure (10%), renal failure 17 (10%), pulmonary alveolar hemorrhage (7%), sepsis (5%), hypoxia (4%), GVHD (4%), gastrointestinal hemorrhage (4%), pneumonia (3%), and pulmonary hemorrhage (3%) (Module 5.3.5.3 Integrated Summary of Safety Table 54).

FDA identified a treatment-emergent SAE for 127 (72%) subjects in the SSP. Table 69 shows the numbers of subjects with an SAE by System Organ Class. Table 70 shows the SAEs by Preferred Term (excluding veno-occlusive liver disease) with an incidence of at least 2%.

**Table 69: SSP – Serious Adverse Events by System Organ Class**

System Organ Class	SSP (n=176)	
Respiratory, thoracic and mediastinal disorders	46	26%
General disorders and administration site conditions	42	24%
Hepatobiliary disorders	38	22%
Infections and infestations	33	19%
Vascular disorders	24	14%
Nervous system disorders	22	13%
Renal and urinary disorders	22	13%
Cardiac disorders	11	6%
Gastrointestinal disorders	11	6%
Immune system disorders	8	5%
Metabolism and nutrition disorders	8	5%
Blood and lymphatic system disorders	7	4%
Neoplasms benign, malignant and unspecified	5	3%
Injury, poisoning and procedural complications	4	2%
Investigations	3	2%
Psychiatric disorders	3	2%
Congenital, familial and genetic disorders	1	1%
Reproductive system and breast disorders	1	1%
Surgical and medical procedures	1	1%

Source: FDA analysis

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

**Table 70: SSP - Serious Adverse Events by Preferred Term**

Preferred Term	SSP (n=176)	
Multi-organ failure	38	22%
Hypotension	20	11%
Respiratory failure	18	10%
Renal failure	17	10%
Pulmonary alveolar hemorrhage	13	7%
Sepsis	8	5%
Gastrointestinal hemorrhage	7	4%
Graft versus host disease	7	4%
Hypoxia	7	4%
Pneumonia	6	3%
Pulmonary hemorrhage	6	3%
Hemorrhage intracranial	5	3%
Hyperuricemia	4	2%
Thrombotic thrombocytopenic purpura	4	2%
Acute respiratory distress syndrome	3	2%
Cardiac arrest	3	2%
Central nervous system hemorrhage	3	2%
Cerebral hemorrhage	3	2%
Convulsion	3	2%
Hepatic failure	3	2%
Infection	3	2%
Lung infiltration	3	2%
Pulmonary edema	3	2%
Renal impairment	3	2%
Septic shock	3	2%

Source: FDA analysis

#### 8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

The applicant did not provide an analysis of discontinuations in the target population. FDA utilized the variable ADISFL in the ISS data file adae.xpt to identify TEAEs leading to discontinuation. There were 39 (22%) subjects in the SSP with such a TEAE. Table 71 shows the TEAEs (excluding veno-occlusive liver disease) resulting in discontinuation for at least 1% of subjects in the SSP. Events in the SMQN Hemorrhage resulted in discontinuation for 13% of the subjects.

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

Due to incomplete characterization of TEAE in Study 99-118, missing data can be assumed, so the majority of the data in Table 71 is specifically from Study 2005-01. There were 37 subjects in Study 2005-01 with a withdrawal event, and the TEAE resulting in withdrawal are shown in Table 71.

**Table 71: SSP – TEAE Resulting in Discontinuation**

Preferred Term	SSP (n=176)		Study 2005-01 (n=102)	
Pulmonary alveolar hemorrhage	6	3%	5	5%
Multi-organ failure	4	2%	4	4%
Hypotension	4	2%	3	3%
Catheter site hemorrhage	3	2%	3	3%
Pulmonary hemorrhage	3	2%	3	3%
Cerebral hemorrhage	2	1%	2	2%
Sepsis	2	1%	2	2%

Source: FDA analysis

#### 8.4.4. Significant Adverse Events

See Section 8.5 for discussions of the AESIs hemorrhage, hypotension and hypersensitivity.

The applicant identified acute GVHD as an additional adverse event of interest. For 2005-01 they reported a lower incidence of TEAE with terms that included GVHD, rash or diarrhea in the treatment arm (32% vs 66%), a lower incidence of TEAE with the terms that included GVHD (8% vs 25%) (Module 5.3.5.3 Integrated Summary of Safety Table 69), and a lower incidence of fatal GVHD (2% vs 6%) (Module 5.3.5.3 Integrated Summary of Safety Table 71). In Pool A, acute GVHD terms were reported for 11% of subjects treated with defibrotide 25 mg/kg/day and in 13% of those treated with 40 mg/kg/day.

***Reviewer Comment: Since there was no specific monitoring in the protocol for acute GVHD, and there were issues with regard to ascertainment of adverse events (See Section 8.3.1), FDA did not consider the data on acute GVHD to be credible, and therefore did not pursue additional analyses. The only conclusion that can be drawn from the available data is that defibrotide did not cause an inordinate amount of fatal acute GVHD.***

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

#### 8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

##### 8.4.5.1. Common Adverse Events

With regard to common adverse events, the applicant reported:

- For Pool A, the most frequent ( $\geq 10\%$ ) TEAEs in subjects treated with defibrotide 25 mg/kg/day included hypotension (37%), diarrhea (24%), multi-organ failure (22%), vomiting (18%), renal failure (17%), nausea (16%), epistaxis (14%) and respiratory failure (11%) (Module 5.3.5.3 Integrated Summary of Safety Table 34).
- For 2005-01, the applicant reported the incidence was at least 5% higher in the treatment group than in the control group for multi-organ failure (15% vs 9%), decubitus ulcer (10% vs 3%), catheter site hemorrhage (9% vs 0%), headache (6% vs 0%) and pulmonary hemorrhage (6% vs 0%) (Study 2005-01 Clinical Study Report Table 46).
- During the prophylaxis phase of 2004, the incidence was at least 5% higher in the prophylaxis group than in the control group only for respiratory failure (7% vs 1%) (Study 2004 Clinical Study Report Table 23).

FDA identified a TEAE for 169 (96%) subjects in the SSP. Table 72 shows the incidence of TEAEs by Preferred Term (excluding veno-occlusive liver disease) that occurred in at least 9 subjects (5%).

**Table 72: SSP – Common TEAE**

Preferred Term	SSP (n=176)	
Hypotension	65	37%
Diarrhea	43	24%
Multi-organ failure	38	22%
Vomiting	31	18%
Renal failure	29	16%
Nausea	28	16%
Epistaxis	24	14%
Respiratory failure	20	11%
Hypertension	17	10%
Hypoxia	17	10%
Pyrexia	17	10%
Agitation	15	9%
Gastrointestinal hemorrhage	15	9%
Hematuria	15	9%

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

**Table 72: SSP – Common TEAE**

Preferred Term	SSP (n=176)	
Pulmonary alveolar hemorrhage	15	9%
Confusional state	13	7%
Exfoliative rash	13	7%
Edema peripheral	13	7%
Pleural effusion	12	7%
Sepsis	12	7%
Abdominal pain	11	6%
Conjunctival hemorrhage	11	6%
Decubitus ulcer	11	6%
Graft versus host disease	11	6%
Sinus tachycardia	11	6%
Bradycardia	10	6%
Catheter site hemorrhage	10	6%
Cough	10	6%
Lung infiltration	10	6%
Edema	10	6%
Post procedural hemorrhage	10	6%
Tachycardia	10	6%
Hematemesis	9	5%
Mental status changes	9	5%
Petechiae	9	5%
Pneumonia	9	5%

Source: FDA analysis

FDA noted a grade 3-5 TEAE for 152 (86%) subjects in the SSP. Table 73 shows the numbers of subjects with a grade 3-5 TEAE by Preferred Term (excluding veno-occlusive liver disease) that occurred in at least 4 subjects (2%). The most common (>5%) grade 4-5 TEAE were multi-organ failure (22%), respiratory failure (10%), renal failure (7%), hypotension (7%), pulmonary alveolar hemorrhage (7%) and hypoxia (6%).

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

**Table 73: SSP – Grades 3 - 5 TEAE**

Preferred Term	SSP (n=176)	
Hypotension	47	27%
Multi-organ failure	38	22%
Renal failure	28	16%
Respiratory failure	20	11%
Hypertension	15	9%
Hypoxia	15	9%
Pulmonary alveolar hemorrhage	15	9%
Diarrhea	11	6%
Sepsis	11	6%
Gastrointestinal hemorrhage	10	6%
Nausea	8	5%
Pneumonia	8	5%
Graft versus host disease	7	4%
Lung infiltration	7	4%
Epistaxis	6	3%
Pleural effusion	6	3%
Pulmonary edema	6	3%
Confusional state	5	3%
Hemorrhage intracranial	5	3%
Pulmonary hemorrhage	5	3%
Thrombocytopenia	5	3%
Catheter site hemorrhage	4	2%
Decreased appetite	4	2%
Febrile neutropenia	4	2%
Hematemesis	4	2%
Hematuria	4	2%
Hemorrhage	4	2%
Hyperuricemia	4	2%
Infection	4	2%
Mental status changes	4	2%
Sinus tachycardia	4	2%

Source: FDA analysis

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

FDA noted a related TEAE for 58 (33%) subjects in the SSP. Table 74 shows the numbers of subjects with a related TEAE by Preferred Term (excluding veno-occlusive liver disease) that occurred in at least 2 subjects (1%).

**Table 74: SSP – Related TEAE**

Preferred Term	SSP (n=176)	
Hypotension	10	6%
Pulmonary alveolar hemorrhage	10	6%
Epistaxis	8	5%
Gastrointestinal hemorrhage	7	4%
Post procedural hemorrhage	5	3%
Diarrhea	4	2%
Catheter site hemorrhage	3	2%
Ecchymosis	3	2%
Nausea	3	2%
Vomiting	3	2%
Central nervous system hemorrhage	2	1%
Cerebral hemorrhage	2	1%
Coagulopathy	2	1%
Conjunctival hemorrhage	2	1%
Hematuria	2	1%
Headache	2	1%
Petechiae	2	1%
Pruritus	2	1%
Pulmonary hemorrhage	2	1%
Rash	2	1%

Source: FDA analysis

#### 8.4.5.2. Dose-Dependency for Adverse Events

The applicant utilized Studies DF-CUP and 99-118 to assess for a relationship between dose and safety outcome. DF-CUP was a compassionate use study of defibrotide for treatment of hepatic VOD with voluntary reporting of adverse events. In this study, treatment with defibrotide was initiated at 10 mg/kg/day and escalated to 25, 40, 60 or 80 mg/kg/day as determined by the investigator. See Section 5.1 for a description of the design of the trial. Table 75 shows the rates of safety events by dose.

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

**Table 75: Study DF-CUP – Summary of Safety Event Rates by Dose**

Safety Event	Defibrotide Dose				
	10 mg/kg/day (n=85)	25 mg/kg/day (n=272)	40 mg/kg/day (n=226)	60/80 mg/kg/day (n=55)	Unknown (n=72)
Any TEAE	59 (69%)	129 (47%)	124 (55%)	27 (49%)	39 (54%)
Any SAE	58 (68%)	123 (45%)	119 (53%)	26 (47%)	38 (53%)
TEAE Leading to Discontinuation	7 (8%)	23 (9%)	25 (11%)	4 (7%)	4 (6%)
TEAE Leading to Death	56 (66%)	120 (44%)	113 (50%)	24 (44%)	37 (51%)
Related TEAE	8 (9%)	23 (9%)	26 (12%)	6 (11%)	6 (8%)
Hemorrhage	9 (11%)	31 (11%)	31 (14%)	8 (15%)	6 (8%)
Hypotension	1 (1%)	1 (<1%)	0	0	0

Source: Study DF-CUP Clinical Study Report Table 14.3.1.1.4

Table 76 shows the numbers of subjects in DF-CUP with TEAE by Preferred Term (excluding veno-occlusive liver disease) by dose that occurred in at least 6 subjects (2%) in the 25 mg/kg/day dose group.

**Table 76: Study DF-CUP – Summary of TEAE by Dose**

Preferred Term	Defibrotide Dose				
	10 mg/kg/day (n=85)	25 mg/kg/day (n=272)	40 mg/kg/day (n=226)	60/80 mg/kg/day (n=55)	Unknown (n=72)
Multi-organ failure	22 (26%)	47 (17%)	41 (18%)	12 (22%)	19 (26%)
Sepsis	8 (9%)	17 (6%)	18 (8%)	3 (5%)	2 (3%)
Graft versus host disease	4 (5%)	13 (5%)	9 (4%)	1 (2%)	1 (1%)
Hemorrhage	0	7 (3%)	5 (2%)	1 (2%)	0
Gastrointestinal hemorrhage	2 (2%)	6 (2%)	6 (3%)	2 (4%)	2 (3%)

Source: FDA analysis

Study 99-118 was a randomized Phase 2 study of two dose levels of defibrotide for treatment of patients with hepatic VOD and MOF. In 99-118, treatment with defibrotide was initiated at 10 mg/kg/day and escalated to 25 or 40 mg/kg/day starting on Day 2 based on randomization. See Section 5.1 for a description of the design of the trial. The applicant noted that there was a slight numerical increase in major safety events in the 40 mg/kg/day cohort. Table 77 shows the rates of safety events by dose.

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

**Table 77: Study 99-118 – Summary of Safety Event Rates by Dose**

Safety Event	Defibrotide Dose	
	25 mg/kg/day (n=74)	40 mg/kg/day (n=75)
Any TEAE	70 (95%)	73 (97%)
Any SAE	50 (68%)	53 (71%)
TEAE Leading to Discontinuation	2 (3%)	4 (5%)
TEAE Leading to Death	41 (55%)	45 (60%)
Related TEAE	12 (16%)	20 (27%)
Grades 3-5 TEAE	67 (91%)	71 (95%)
Hemorrhage	36 (49%)	43 (57%)
Hypotension	25 (34%)	30 (40%)

Source: Study 99-118 Clinical Study Report Table 14.3.1.1

Table 78 shows the numbers of subjects in 99-118 with any-grade TEAE by Preferred Term (excluding veno-occlusive liver disease) by dose with a risk difference at least 5% greater at the higher dose level. The higher dose level also had a substantially higher incidence of grade 3-5 gastrointestinal hemorrhage (20% vs 7%) and grade 3-5 hypoxia (31% vs 19%).

**Table 78: Study 99-118 – Summary of TEAE by Dose**

Preferred Term	Defibrotide Dose		Risk Difference
	25 mg/kg/day (n=74)	40 mg/kg/day (n=75)	
Gastrointestinal hemorrhage	7 (9%)	18 (24%)	15%
Hypoxia	15 (20%)	25 (33%)	13%
Exfoliative rash	13 (18%)	20 (27%)	9%
Dyspnea	4 (5%)	10 (13%)	8%
Hemorrhage	5 (7%)	11 (15%)	8%
Renal failure	24 (32%)	30 (40%)	8%
Sepsis	2 (3%)	7 (9%)	7%
Thrombocytopenia	7 (9%)	12 (16%)	7%
Hypotension	25 (34%)	30 (40%)	6%
Abdominal pain	7 (9%)	11 (15%)	5%
Pleural effusion	7 (9%)	11 (15%)	5%

Source: FDA analysis

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

Triplett et al (2015) conducted a single-arm trial of defibrotide for treatment of children with hepatic VOD using an inpatient escalation from 10 mg/kg/day to as high as 110 mg/kg/day. Platelets were maintained at  $\geq 20$  Gi/L with transfusions. Patients were monitored for adverse events through 14 days after the last dose of study drug. The 34 children treated had a median age of 8 years (range, 0.5 – 22 years). Nineteen (56%) had MOF at enrollment, and 10 patients developed MOF during treatment. The median peak defibrotide dose was 60 mg/kg/day (range, 6.25 – 110 mg/kg/day), and the median duration of defibrotide therapy was 15 days (range, 1 to 102 days). Reasons for stopping defibrotide included resolution of VOD (56%), death (29%), lack of response (12%), and transition to palliative care (3%). The exposure-adjusted rates of bleeding and hypotension are shown in Table 79.

**Table 79: NCT 00143546 – Exposure-Adjusted Safety Event Rates by Dose**

Defibrotide Daily Dose	Patient-Days	Bleeding (Events per 100 patient-days)	Hypotension (Events per 100 patient-days)
$\leq 25$ mg/kg/day	101	3	5
25.1 – 59.9 mg/kg/day	175	4	3
60 mg/kg/day	286	3	1
60.1 – 100 mg/kg/day	112	2	2
>100 mg/kg/day	38	13	2

Source: Adapted from Triplett, Kuttub, et al. 2015

**Reviewer Comment: The available data are supportive of bleeding being a dose-related toxicity.**

#### 8.4.5.3. Time-Dependency for Adverse Events

The applicant conducted an analysis of TEAE by duration of exposure. Table 80 shows the summary of safety events by dose and duration of exposure in Pool A. The sponsor cautioned that interpretation was limited by nonrandom reasons for a shorter vs longer duration of therapy that might impact the occurrence of TEAEs, but they concluded that overall there were no meaningful correlations between TEAE incidence and dose duration (Module 2.7.4 Summary of Clinical Safety Section 5.2).

**Table 80: Pool A – Summary of Safety Event Rates by Duration of Treatment**

Overall summary of TEAEs, n (%)	Defibrotide 25 mg/kg		Defibrotide 40 mg/kg	
	≤21 days	>21 days	≤21 days	>21 days
Number of patients	92	84	41	34
At least 1 TEAE	88 (95.7)	81 (96.4)	40 (97.6)	33 (97.1)
At least 1 very common (≥10%) TEAE	71 (77.2)	67 (79.8)	39 (95.1)	33 (97.1)
At least 1 severe or life-threatening TEAE	64 (69.6)	63 (75.0)	39 (95.1)	29 (85.3)
At least 1 treatment-related TEAE <sup>a</sup>	34 (37.0)	24 (28.6)	10 (24.4)	10 (29.4)
At least 1 TEAE of special interest (hemorrhage and/or hypotension)	61 (66.3)	59 (70.2)	25 (61.0)	29 (85.3)
At least 1 hemorrhage	51 (55.4)	50 (59.5)	17 (41.5)	26 (76.5)
At least 1 hypotension	25 (27.2)	40 (47.6)	17 (41.5)	13 (38.2)
At least 1 TEAE leading to death <sup>b</sup>	62 (67.4)	44 (52.4)	30 (73.2)	15 (44.1)
At least 1 acute GVHD	4 (4.3)	15 (17.9)	5 (12.2)	5 (14.7)
At least 1 serious TEAE	74 (80.4)	56 (66.7)	31 (75.6)	22 (64.7)

Source: Module 5.3.5.3 Integrated Summary of Safety Table 92

**Reviewer Comment: I agree with the applicant that the results are confounded by the nonrandomness of dropout before day 21.**

#### 8.4.6. Results of Safety Tests

##### 8.4.6.1. Laboratory Findings

The applicant assessed laboratory abnormalities by protocol. They concluded that “there were no safety concerns for defibrotide revealed from clinical laboratory results” (Module 5.3.5.3 Integrated Summary of Safety Section 5.1). The applicant made several observations by protocol from their analysis of laboratory data:

- For comparisons between the defibrotide treatment group and the historical controls in Study 2005-01, the applicant concluded that there were no important differences between the study groups in change from baseline to study completion or hospital discharge for results of renal or hepatic function tests (Module 5.3.5.3 Integrated Summary of Safety Section 5.2).
- For Study 99-118, in both dose cohorts, there was an increase in mean serum creatinine and total bilirubin for the study population overall. Shifts from normal to abnormal were observed in a minority of the subjects for several of the analytes, but there was no consistent relationship between dose-level and proportion of subjects with such a shift (Module 5.3.5.3 Integrated Summary of Safety Section 5.3).

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

- During the prophylaxis phase of Study 2004, there was a numerically higher incidence of total bilirubin > 10 mg/dL in the prophylaxis group than in the control group (3% vs <1%), but there were etiologies other than study drug for all subjects who experienced such high bilirubin levels. There were no other substantial differences between the study arms reported for laboratory abnormalities (Module 5.3.5.3 Integrated Summary of Safety Section 5.4).

Laboratory results in the ISS data set were used for the analysis by FDA. The severity was coded by this reviewer according to CTCAE version 4 for key laboratory tests. Table 81 shows the incidence of grades 3-4 worst post baseline abnormalities in key laboratory tests in the SSP as well as for the two study groups in Study 2005-01. Results for all analytes were not collected on every protocol, so Table 81 shows results only when available in the population or study identified in the column header. It is acknowledged that as a result of the natural history of the disease, a substantial proportion of subjects with hepatic VOD and MOF will have laboratory abnormalities. Study 2004, the prophylaxis study, provides an alternative population with at least short-term follow-up largely free of major comorbidities. Table 81 also shows the incidence of grades 3-4 worst post baseline abnormalities for key laboratory tests in Study 2004 on Days 1-14, a period largely prior to onset of regimen-related toxicities and GVHD.

**Table 81: Key Grades 3 – 4 Laboratory Abnormalities**

Laboratory Abnormality	SSP (n=176)	Study 2005-01		Study 2004 Days 1-14	
		Defibrotide- Treated (n=102)	Control Group (n=32)	Defibrotide Prophylaxis (n=1)	Control Group (n=1)
<i>Chemistry Tests</i>					
Albumin low		20 (20%)	9 (28%)	1 (<1%)	0
Alkaline phosphatase elevated		5 (5%)	3 (9%)	0	0
ALT elevated		41 (40%)	13 (41%)	1 (<1%)	1 (<1%)
AST elevated		55 (54%)	16 (50%)	1 (<1%)	0
Bilirubin elevated	163 (93%)	94 (92%)	30 (94%)	5 (3%)	2 (1%)
Creatinine elevated	48 (27%)	29 (28%)	10 (31%)	0	0
Creatinine clearance low		41 (40%)	10 (31%)		
Potassium elevated		5 (5%)	3 (9%)		
Potassium low		53 (52%)	16 (50%)		
Sodium elevated		12 (12%)	6 (19%)		
Sodium low		33 (32%)	11 (34%)		
<i>Hematology Tests</i>					
Hemoglobin low	78 (44%)	53 (52%)	19 (59%)		
Neutrophils low <sup>a</sup>		53 (52%)	24 (75%)		
Platelets low <sup>a</sup>	124 (70%)	72 (71%)	26 (81%)	28 (16%)	8 (5%)

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

**Table 81: Key Grades 3 – 4 Laboratory Abnormalities**

Laboratory Abnormality	SSP (n=176)	Study 2005-01		Study 2004 Days 1-14	
		Defibrotide- Treated (n=102)	Control Group (n=32)	Defibrotide Prophylaxis (n=1)	Control Group (n=1)
<i>Coagulation Tests</i>					
aPTT elevated	44 (25%)	32 (31%)	7 (22%)	2 (1%)	2 (1%)
PT elevated	12 (7%)	8 (8%)	2 (6%)	1 (<1%)	2 (1%)
Fibrinogen low	6 (3%)	6 (6%)	1 (3%)	0	0

Source: FDA analysis

<sup>a</sup>Grade 4 only

Over 90% of the subjects in the SSP had an elevated total bilirubin (Table 81). However, when comparing the defibrotide-treated vs the control group in Study 2005-01, there was no difference in the incidence of grade 3-4 elevated bilirubin (92% vs 94%, respectively), and no adverse difference for maximum bilirubin >10 mg/dL (57% vs 81%, respectively). During the first 14 days of Study 2004, the prophylaxis trial, few subjects on either the defibrotide or the control arm had a grade 3-4 elevated bilirubin (3% vs 1%). Given the high background rate of abnormalities in bilirubin and transaminases after HSCT, especially in patients with VOD, an assessment for Hy's law cases was not conducted.

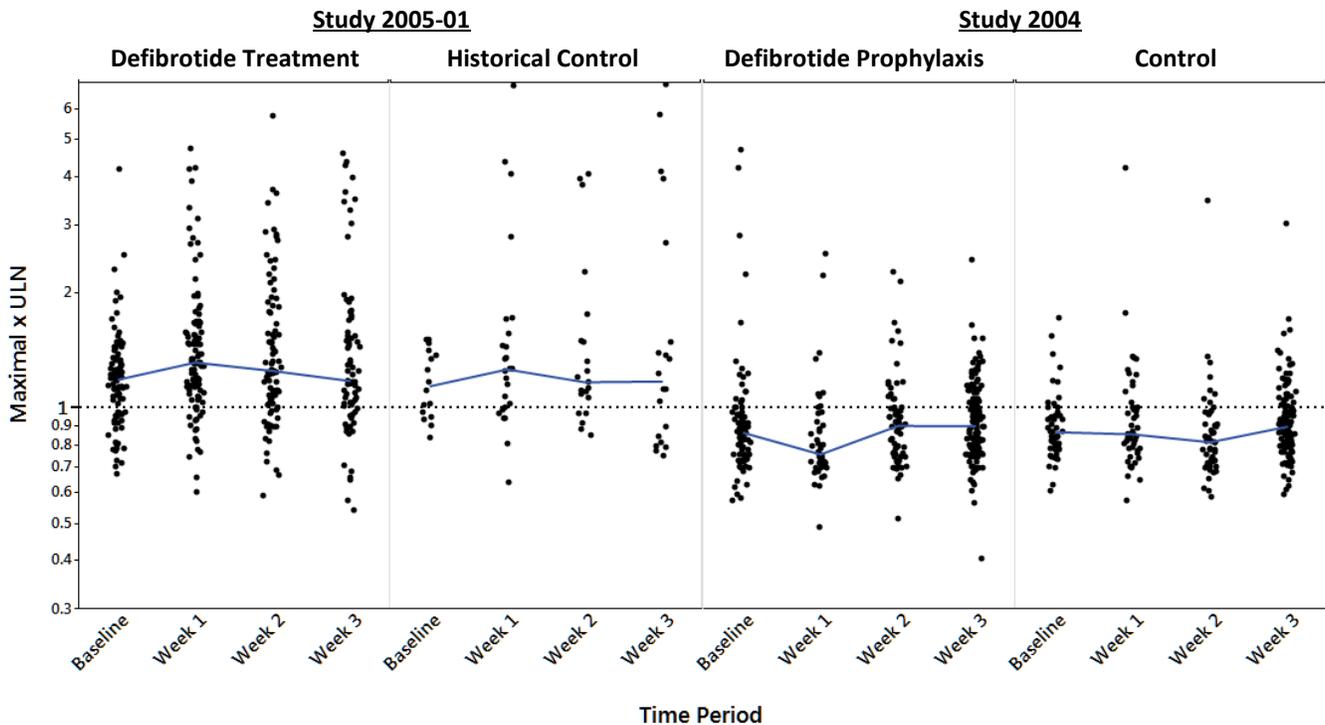
***Reviewer Comment: The available data do not demonstrate that any chemistry abnormalities were caused by defibrotide.***

A grade 3-4 elevation in aPTT occurred in 25% of subjects in the SSP. This was the only key laboratory test with a substantially higher rate in the defibrotide-treated group than in the control group in Study 2005-01 (31% vs 22%, respectively) (Table 81), raising a question of whether defibrotide increased the aPTT. Figure 9 shows the results of serial measurements of aPTT over the first 3 weeks of treatment or prophylaxis in Studies 2005-01 and 2004. Extreme outliers were seen in both defibrotide groups and in the controls, but the population median in the defibrotide groups was not consistently higher than baseline after start of study drug, supporting no causal relationship between defibrotide and the elevated aPTT. In addition, in Study 99-118, there was no dose-related trend in the incidence of grade 1-4 or grade 3-4 elevation of aPTT when assessed weekly over the first 3 weeks.

Clinical Review  
 Tanya Wroblewski, M.D.  
 Donna Przepiorka, M.D. Ph.D.  
 NDA 208114  
 Defitelio (Defibrotide Sodium)

**Figure 10: Studies 2005-01 and 2004 - Serial Measurements of aPTT**

aPTT values shown as maximal multiple of the upper limit of normal (x ULN) at baseline (days -21 to 1), Week 1 (days 2 to 7), Week 2 (days 8-14) and Week 3 (days 15 to 21). The blue solid line represents the median of the population at the time period. The dotted line is 1x ULN.



Source: FDA analysis

**Reviewer Comment:** *The available data do not demonstrate that any coagulation abnormalities were caused by defibrotide, but a meaningful analysis for a cumulative effect after more than 21 days of treatment could not be performed due to confounding by the disease process.*

Given that defibrotide is administered early after HSCT when used to treat patients with hepatic VOD, any effect on hematopoiesis might be manifested as either a primary or secondary graft failure, depending on the timing of start of therapy. As shown in Table 81, a substantial proportion of subjects in the SSP had severe or life-threatening cytopenias, but these data do not distinguish between usual events in the HSCT recovery period, effects of the natural history of hepatic VOD, and a potential toxicity of defibrotide.

For Study 2005-01, the applicant reported neutrophil engraftment by Day +100 after HSCT for 87% in the defibrotide arm and 81% in the historical control group. The median time to

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

neutrophil recovery was 17 days vs 21 days, respectively (Study 2005-01 Clinical Study Report Table 92). For Study 2004, the applicant reported there was no difference between the defibrotide prophylaxis arm and the control arm in graft failure at Day +30 (1% vs 2%, respectively) or at Day +100 (6% vs 5%, respectively) after HSCT (Study 2004 Clinical Study Report Table 14.2.19). Time to hematopoietic recovery was not assessed in Study 2004.

Maximova N, Pizzol A, et al (2015) reported a retrospective review of 22 children treated with defibrotide 25 mg/kg/day as prophylaxis against hepatic VOD after HSCT and compared hematopoietic recovery to an additional 22 children transplanted without defibrotide prophylaxis. They reported that the group in which defibrotide was used had a numerically longer median time to recovery of neutrophils to  $>0.5$  Gi/L (21 days vs 15 days,  $p<0.01$ ), recovery of platelets to 50 Gi/L (33 days vs 27 days), and recovery of reticulocytes to  $>2\%$  (43 days vs 40 days). There were no differences between the two groups in incomplete chimerism or infections.

***Reviewer Comment: The findings of Maximova et al that defibrotide delayed neutrophil recovery when used as prophylaxis are of interest, but this is a single, small retrospective study that did not adjust for the factors that might affect the time to hematopoietic recovery. Moreover, a clinically meaningful effect of defibrotide on graft failure was not seen in Studies 2005-01 or Study 2004. Overall, the totality of the evidence is inconsistent. A more carefully conducted comparative trial is needed to address the signal raised by Maximova et al.***

#### 8.4.6.2. Vital Signs

Study 2005-01 was the only protocol in patients with VOD which required serial vital signs during treatment with defibrotide. For this study, vital signs were to be recorded daily during the treatment period and at Day +100 after HSCT and Day +180 after HSCT. The period of vital sign collection for the historical controls was not described in detail in the clinical study report. The differences between study groups as described by the applicant included (Study 2005-01 Clinical Study Report Section 12.5):

- A higher proportion of the control group had diastolic blood pressure measurements  $>100$  mm Hg than defibrotide-treated subjects (19% vs 6%).
- A higher proportion of the control group compared to defibrotide-treated subjects had temperature  $<36^{\circ}\text{C}$  (44% vs 18%) and  $>39^{\circ}\text{C}$  (44% vs 28%).
- Median decreases in systolic blood pressure (mm Hg) were greater in the control group than in the defibrotide group at study completion/hospital discharge (-10 vs -1) and at Day +100 (-22 vs -6).
- Median decreases in heart rate were greater in the control group compared to the defibrotide group at study completion/hospital discharge (-40 vs -15).

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

Table 82 shows the results of the Sponsor’s outlier analysis of the vital signs for Study 2005-01. Weight was the only vital sign recorded for Study 2004, so no comparative analysis was conducted for that study.

**Table 82: Study 2005-01 – Vital Sign Outlier Analysis**

Parameter, (n (%))	Defibrotide	Historical Control
N	102	32
At least 1 clinically significant vital sign measurement during study:	97 (95.1)	31 (96.9)
<b>At least 1 clinically significant vital sign measurement by category during study:</b>		
Systolic blood pressure		
<60 mmHg	5 (4.9)	1 (3.1)
>160 mmHg	16 (15.7)	6 (18.8)
Diastolic blood pressure		
<50 mmHg	71 (69.6)	22 (68.8)
>100 mmHg	6 (5.9)	6 (18.8)
Heart rate		
<40 beats/minute	2 (2.0)	1 (3.1)
>120 beats/minute	75 (73.5)	26 (81.3)
Respiratory rate		
<10 breaths/minute	7 (6.9)	4 (12.5)
>40 breaths/minute	38 (37.3)	10 (31.3)
Body temperature		
<36°C	18 (17.6)	14 (43.8)
>39°C	29 (28.4)	14 (43.8)

Source: Study 2005-01 Clinical Study Report Table 94

**Reviewer Comments:**

- ***Given the nonrandomized nature of the study groups and the potential for asynchrony between groups for recording data, the comparative analysis should be considered exploratory.***
- ***Since vital signs were done only “daily,” potential infusion reactions may have been missed. The incompleteness of this data warrants a comparative trial to objectively characterize the risks of serious deviations in vital signs, such as hypotension, during treatment with defibrotide.***

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

#### 8.4.6.3. Electrocardiograms (ECGs)

**Table 83: Study R09-1425 – Time-Averaged Analyses for ECG Intervals**

	Treatment Group			
	Defibrotide 6.25 mg/kg	Defibrotide 15 mg/kg	Placebo	Moxifloxacin 400 mg
Total N	52	52	51	52
Heart Rate in bpm (mean change from baseline)	3.5	3.4	3.1	4.3
Heart Rate tachycardic outliers N (%)	0	1 (2%)	0	1 (2%)
Heart Rate bradycardic outliers N (%)	0	1 (2%)	0	0
PR in ms (mean change from baseline)	-1.5	-1.9	-2.7	-3.0
PR outliers N (%)	0	0	0	1 (2%)
QRS in ms (mean change from baseline)	-0.3	-0.4	-0.1	-0.5
QRS outliers N (%)	0	0	0	0
QT in ms (mean change from baseline)	-11.7	-11.2	-10.8	-4.1
QT new >500 ms N (%)	0	0	0	0
QTcI in ms (mean change from baseline)	-5.0	-4.6	-4.9	4.6
QTcI new >500 ms N (%)	0	0	0	0
QTcI new >480 ms N (%)	0	0	0	0
QTcI >30-60 ms increase N (%)	0	1 (2%)	1 (2%)	0
QTcI >60 ms increase N (%)	0	0	0	0
QTcF in ms (mean change from baseline)	-4.5	-4.4	-4.7	4.5
QTcF new >500 ms N (%)	0	0	0	0
QTcF new >480 ms N (%)	0	0	0	0
QTcF >30-60 ms increase N (%)	0	1 (2%)	0	0
QTcF >60 ms increase N (%)	0	0	0	0
QTcB in ms (mean change from baseline)	-0.9	-0.9	-1.6	9.0
QTcB new >500 ms N (%)	0	0	0	0
QTcB new >480 ms N (%)	1 (2%)	1 (2%)	0	0
QTcB >30-60 ms increase N (%)	5 (10%)	6 (12%)	2 (4%)	9 (17%)
QTcB >60 ms increase N (%)	0	0	1 (2%)	0
New abnormal U waves N (%)	0	0	0	0
New ST segment depression changes N (%)	3 (6%)	1 (2%)	1 (2%)	0
New ST segment elevation changes N (%)	0	0	0	0
New T wave inverted N (%)	1 (2%)	1 (2%)	4 (8%)	7 (13%)
New 2 <sup>nd</sup> and 3 <sup>rd</sup> Degree Heart Block, Complete RBBB & LBBB, MI N (%)	0	0	0	0

Source: Study R09-1425 Clinical Study Report Table 12.5.2.1-1

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

Serial ECGs were required only for Studies R09-1425 and 2012-03-PKREN. R09-1425 was a randomized, placebo-controlled, single-dose, four-period cross-over study comparing ECG effects of defibrotide at 6.25 mg/kg iv, defibrotide 15 mg/kg iv and moxifloxacin 400 mg orally in 52 healthy volunteers. ECGs were acquired from a continuous Holter recording at 45, 30, and 15 minutes prior to dosing and 1, 2, 2.25, 2.5, 2.75, 3, 3.5, 4, 6, 12, 18, and 23 hours after dosing. The results are shown in Table 83. The sponsor identified no safety signal on the basis of central tendency, outlier analysis, or exposure effect modeling. The Clinical Pharmacology reviewer (Dr. Guoxiang Shen) concluded that defibrotide has no effect on heart rate, AV conduction, or cardiac depolarization.

In 2012-03-PKREN, singlet ECGs were performed at baseline and 2 days after dosing with defibrotide 6.25 mg/kg iv in 6 subjects on dialysis, and at baseline and 1 day after completion of 4 doses of defibrotide 6.25 mg/kg every 6 hours for 6 subjects with severe renal insufficiency and 6 healthy volunteers. The sponsor reported that there were no clinically significant findings in the ECGs (Study 2012-03-PKREN Clinical Study Report Section 12.5.3), but no statistical analyses were performed. In an analysis of outliers by FDA, the only positive finding was a single subject with severe renal insufficiency who developed a new QTcF >480 msec with an increase from baseline >60 msec. Since the ECGs were not taken during an expected period of maximal concentration of defibrotide, the data as collected for 2012-03-PKREN are not sufficient to exclude an effect of defibrotide on cardiac conduction, and no further analyses were pursued by this reviewer.

***Reviewer Comment: I agree with the Clinical Pharmacology reviewer's conclusion that defibrotide has no clinically meaningful effects on cardiac conduction based on the results of Study R09-1425.***

#### 8.4.6.4. QT

See Section 8.4.6.3 for a discussion of the thorough QT study (R09-142). On the basis of their re-analysis of the data, the Interdisciplinary Review Team determined that defibrotide doses of 6.25 mg/kg and 15 mg/kg had no significant QTc prolongation effect (Interdisciplinary Review Team Consultation Review dated 2/8/2016).

#### 8.4.6.5. Immunogenicity

The sponsor conducted no formal studies of anti-defibrotide antibodies (Response to Information Request received 10/30/2015). They provided the following additional rationale for concluding that there is no risk of immunogenicity:

- No antidefibrotide antibodies were detected in the nonclinical toxicology studies, albeit using a nonvalidated assay.

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

- In the assessment of PK in 9 evaluable subjects in Study 99-118, there were no changes in clearance over time that might indicate the presence of neutralizing antibodies.
- In Study CS001/03, a 5-day PD study using a pre-1995 version of defibrotide in patients with peripheral artery disease, 1 of 14 subjects developed treatment-emergent anti-DS-DNA and anti-SS-DNA antibodies (3 months after treatment with defibrotide) vs none of the 11 subjects treated with placebo.
- The applicant found no unequivocal reports of hypersensitivity to defibrotide in patients treated for hepatic VOD in the safety database.
- Patients being treated for hepatic VOD with MOF have received high-dose chemotherapy and are therefore immunocompromised with low risk for developing an antibody response.

FDA also noted that in Study HL-12326, a 3-day PD study using [REDACTED] (b)(4) defibrotide in healthy volunteers, none of 18 subjects who received defibrotide had anti-DS-DNA detected through study day 14.

***Reviewer Comment: The reports of immunogenicity for other drugs in this chemical class supports the potential for development of anti-defibrotide antibodies. Although a memory antibody response is certainly possible in the posttransplant period as demonstrated by complications in patients who have received ABO-mismatched allografts, I agree that the risk is low in the current intended population. However, it is incumbent upon the sponsor to provide data to confirm that conclusion, and I therefore recommend that future studies of defibrotide include an assessment of immunogenicity to address this question.***

#### 8.4.7. Safety in Special Populations

##### 8.4.7.1. Safety in Pediatric Patients

The applicant noted the following observations in the assessment of safety outcomes by age for the 25 mg/kg/day dose in Pool A (Module 5.3.5.3 Integrated Summary of Safety Section 8.2.1):

- Pediatric patients ( $\leq 16$  years old) had a lower incidence of fatal TEAE than adults (49% vs 67%) but more treatment-related TEAE (45% vs 26%).
- The pediatric cohort had less multi-organ failure (14% vs 26%), less renal failure (6% vs 23%), but more pulmonary alveolar hemorrhage (15% vs 5%).

In addition, the assessment within the pediatric cohort in Pool A by dose (25 mg/kg/day (n=65) vs 40 mg/kg/day (n=24)) (Module 5.3.5.3 Integrated Summary of Safety Section 8.2.1) showed:

- The higher dose was associated with a higher incidence of common TEAE (100% vs 74%), severe TEAE (96% vs 74%), fatal TEAE (58% vs 49%), hemorrhage (67% vs 59%), and hypotension (54% vs 34%).

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

- The higher dose was associated with more thrombocytopenia (21% vs 5%), more multi-organ failure (25% vs 14%), more gastrointestinal hemorrhage (21% vs 8%), more renal failure (21% vs 6%), more hypoxia (38% vs 6%), and more exfoliative rash (29% vs 6%).

Table 84 provides a summary of safety events by age within the pediatric cohort in Pool A. There were no age-related trends in major safety events (Table 84). At the Preferred Term level, comparing infants vs children vs adolescents, there was a trend for an inverse relationship with age for respiratory failure (8% vs 4% vs 2%), pulmonary hemorrhage (7% vs 2% vs 2%) and the SAE pulmonary alveolar hemorrhage (7% vs 2% vs 2%) (Module 5.3.5.3 Integrated Summary of Safety Tables 80 and 81).

**Table 84: Pool A – Summary of Safety Event Rates Within the Pediatric Cohort By Age**

Overall summary of TEAEs, n (%)	Defibrotide 25 mg/kg			Defibrotide 40 mg/kg			Historical Control		
	0-23m	2-11y	12-16y	0-23m	2-11y	12-16y	0-23m	2-11y	12-16y
Number of patients	22	29	14	9	11	4	5	7	2
At least 1 TEAE	21 (95.5)	26 (89.7)	14 (100.0)	9 (100.0)	11 (100.0)	4 (100.0)	5 (100.0)	7 (100.0)	2 (100.0)
At least 1 very common (≥10%) TEAE	20 (90.9)	17 (58.6)	11 (78.6)	9 (100.0)	11 (100.0)	4 (100.0)	5 (100.0)	5 (71.4)	1 (50.0)
At least 1 severe or life-threatening TEAE	18 (81.8)	19 (65.5)	11 (78.6)	9 (100.0)	10 (90.9)	4 (100.0)	NA	NA	NA
At least 1 treatment-related TEAE <sup>a</sup>	7 (31.8)	13 (44.8)	9 (64.3)	3 (33.3)	3 (27.3)	1 (25.0)	NA	NA	NA
At least 1 TEAE of special interest (hemorrhage and/or hypotension)	15 (68.2)	16 (55.2)	12 (85.7)	9 (100.0)	7 (63.6)	4 (100.0)	4 (80.0)	6 (85.7)	2 (100.0)
At least 1 hemorrhage	13 (59.1)	15 (51.7)	10 (71.4)	6 (66.7)	6 (54.5)	4 (100.0)	3 (60.0)	6 (85.7)	2 (100.0)
At least 1 hypotension	9 (40.9)	6 (20.7)	7 (50.0)	8 (88.9)	3 (27.3)	2 (50.0)	2 (40.0)	2 (28.6)	0
At least 1 TEAE leading to death <sup>b</sup>	16 (72.7)	9 (31.0)	7 (50.0)	6 (66.7)	4 (36.4)	4 (100.0)	2 (40.0)	6 (85.7)	0
At least 1 acute GVHD	3 (13.6)	1 (3.4)	1 (7.1)	0	2 (18.2)	2 (50.0)	2 (40.0)	2 (28.6)	1 (50.0)
At least 1 serious TEAE	17 (77.3)	17 (58.6)	10 (71.4)	8 (88.9)	5 (45.5)	4 (100.0)	NA	NA	NA

Source: Module 5.3.5.3 Integrated Summary of Safety Table 79

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

Table 85 shows the numbers of subjects in the SSP with a TEAE by Preferred Term (excluding veno-occlusive liver disease) by age. The terms are listed in decreasing order of risk difference between age groups. Only terms with an absolute risk difference  $\geq 5\%$  are shown. The risk difference was greatest for pulmonary hemorrhage.

**Table 85: SSP – TEAE By Age Group**

Preferred Term	Age <17 years (n=65)		Age $\geq 17$ years (n=111)		Risk Difference
Pulmonary alveolar hemorrhage	10	15%	5	5%	11%
Pulmonary hemorrhage	6	9%	1	1%	8%
Hypertension	9	14%	8	7%	7%
Hematemesis	6	9%	3	3%	7%
Hematuria	8	12%	7	6%	6%
Bradycardia	6	9%	4	4%	6%
BK virus infection	4	6%	1	1%	5%
Graft versus host disease	2	3%	9	8%	-5%
Sinus tachycardia	2	3%	9	8%	-5%
Infection	0	0	6	5%	-5%
Hypoxia	4	6%	13	12%	-6%
Nausea	8	12%	20	18%	-6%
Sepsis	2	3%	10	9%	-6%
Decubitus ulcer	1	2%	10	9%	-7%
Confusional state	1	2%	12	11%	-9%
Edema peripheral	1	2%	12	11%	-9%
Multi-organ failure	9	14%	29	26%	-12%
Renal failure	4	6%	25	23%	-16%

Source: FDA analysis

The results of Study 2004, the prevention trial, were used to further clarify the risk of pulmonary hemorrhage in children. The applicant reported that during the prophylaxis phase (i.e., prior to development of VOD), subjects on the defibrotide arm had a higher incidence of respiratory failure (7% vs 1%), but there was no difference between arms in pulmonary hemorrhage (1% vs 0%) or pulmonary alveolar hemorrhage (1% on both arms) (Study 2004

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

Clinical Study Report Section 12.2). None of the respiratory failure events was considered drug-related. In addition, there were no age-related trends for respiratory failure, pulmonary hemorrhage or pulmonary alveolar hemorrhage among the pediatric subjects who received defibrotide prophylaxis (Study 2004 Clinical Study Report Table 14.3.1.2.3).

**Reviewer Comment: Overall, the safety profile in children was similar to that in adults, and the results of FDA's evaluation by Preferred Term was consistent with the findings reported by the applicant. The only potential safety signal in the pediatric population was for pulmonary bleeding. However, the numbers of events are small, and the results from Study 2004 did not confirm the risk, so firm conclusions cannot be made.**

#### 8.4.7.2. Safety in Geriatric Patients

The applicant identified 12 subjects > 65 years old in Pool B, only three of whom were treated for hepatic VOD with MOF after HSCT. The number of geriatric subjects was too small for a meaningful analysis of safety outcomes.

#### 8.4.7.3. Drug-Demographic Interactions

The applicant assessed major safety events, TEAE and AESI in Pool A by age, gender, race, and body mass, and in Pool B by weight. Safety outcomes in specific age groups are discussed in Sections 8.4.7.1 and 8.4.7.2. For the remaining demographic factors, they reported no clinically meaningful trends except that in comparison to females, male subjects had more related TEAE (38% vs 25%) and more related gastrointestinal hemorrhage (7% vs 0%) (Module 5.3.5.3 Integrated Summary of Safety Section 8.1). In the applicant's nonrandomized comparison of TEAEs by treatment group vs historical controls in Study 2005-01, the incidence of hemorrhage events, including gastrointestinal hemorrhage, was also higher in males than in females within the control group (Study 2005-01 Clinical Study Report Section 12.3.6.5).

In a comparison of TEAE by race in the SSP, FDA found that the only Preferred Term (excluding veno-occlusive liver disease) with an absolute difference of at least 10% between caucasians and subjects of other races was cough (2% vs 18%, respectively). In a comparison of TEAE in the SSP by gender, males had a higher incidence of renal failure (21% vs 10%) and multi-organ failure (26% vs 15%). The trend for the increase in renal failure and multi-organ failure in males was not consistent in the subgroup Other Defibrotide-Treated Patients, including those with hepatic VOD with multi-organ failure treated with the 25 mg/kg/day dose. The FDA analysis showed no other substantial differences in TEAE by race or gender.

**Reviewer Comment: There is no consistent safety signal of concern in any demographic subgroup.**

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

#### 8.4.7.4. Drug-Disease Interactions

The applicant assessed major safety events, TEAE and AESI in Pool A by dialysis dependence at study entry, ventilator dependence at study entry, primary disease for HSCT, transplant type and prior HSCT. They noted the following trends for the defibrotide-treated subjects (Module 5.3.5.3 Integrated Summary of Safety Section 8.2):

- There was a modestly higher incidence of TEAEs and major safety events in subjects who were dialysis-dependent, ventilator-dependent, dialysis- or ventilator-dependent, or who had undergone allogeneic HSCT.
- Dialysis-dependence was associated with a higher risk of hypotension, hemorrhage events, severe epistaxis, respiratory failure and pulmonary alveolar hemorrhage.
- Ventilator-dependence was associated with a higher risk of hypotension, pulmonary alveolar hemorrhage, agitation, pyrexia, bradycardia, conjunctival hemorrhage, hypothermia, post-procedural hemorrhage, hematuria, epistaxis and petechiae.
- Allogeneic HSCT was associated with a higher risk of hemorrhage events and hypotension.

In the applicant's assessment of TEAEs in the historical controls from Study 2005-01, the incidence of hemorrhage events and hypotension were also higher in subjects by dialysis-dependence or ventilator-dependence within the control group alone for some analyses (Study 2005-01 Clinical Study Report Tables 14.3.1.19.7.1, 14.3.1.19.7.2, 14.3.1.22.7.1 and 14.3.1.22.7.1).

In Study 2012-03-PKREN, 6 subjects on chronic hemodialysis were exposed to a single infusion of defibrotide 6.25 mg/kg on a nondialysis day (Day 1) and a single infusion of defibrotide 6.25 mg/kg on a dialysis day (Day 4). Only 1 TEAE was reported in this population. One subject had grade 1 vomiting less than one hour from the initiation of infusion of defibrotide on Day 1. The TEAE resolved without a change in dosing, and it did not recur with the second dose on Day 4. Six subjects with severe renal insufficiency (eGFR < 30 mL/min/1.73 m<sup>2</sup>) received defibrotide 6.25 mg/kg iv every 6 hours for 4 doses. There were no TEAE reported for this group within the one week follow-up period.

FDA's analyses of the SSP confirmed that subjects who were dialysis- or ventilator-dependent at study entry had a higher risk of Hemorrhage\_SMQN (71% vs 55%). Further, hypotension was the only Preferred Term with at least 20% greater incidence in those who were dialysis- or ventilator-dependent (57% vs 31%). In FDA's comparison by HSCT type, the risk difference was  $\geq 20\%$  in allogeneic HSCT recipients than in autologous recipients for the Preferred Term hypotension (40% vs 15%) and for Acute renal failure\_SMQN (22% vs 0%).

***Reviewer Comment: The differences in the risks of TEAE by the subgroup factors noted are consistent with the factors themselves (i.e., patients on dialysis acutely could be expected to have a higher rate of complications than those not on dialysis). Although this is confirmed by***

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

***the applicant's comparison of safety outcomes within the historical controls in Study 2005-01, such a comparison is only exploratory. Comparisons from a randomized trial would have more credibility. The safety results from Study 2012-03-PKREN provide limited information that supports the safety of defibrotide in patients with renal insufficiency or on dialysis.***

#### 8.4.7.5. Safety Findings in the Healthy Volunteers

In Study 2012-03-PKREN, 6 healthy volunteer received defibrotide 6.25 mg/kg iv every 6 hours for 4 doses. There were no TEAE reported, and there were no notable laboratory abnormalities (Study 2012-03-PKREN Clinical Study Report Section 12).

In Study R09-1425, 52 healthy volunteers received placebo, defibrotide 6.25 mg/kg iv, defibrotide 15 mg/kg iv or moxifloxacin 400 mg PO in a cross-over fashion with a wash-out of at least 3 days. There were no deaths or SAEs. TEAE were reported for 5 (10%) subjects after placebo, 7 (13%) subjects after defibrotide 6.25 mg/kg and 1 (2%) subject after defibrotide 15 mg/kg (Study R09-1425 Clinical Study Report Section 12). Excluding venipuncture events, there were no TEAE that occurred in more than 1 subject per group. TEAEs reported as related included diarrhea with defibrotide 6.25 mg/kg, and nausea, feeling hot and hyperhidrosis with placebo. All TEAEs were considered mild. No clinically significant laboratory abnormalities were reported (Study R09-1425 Clinical Study Report Section 12).

***Reviewer Comment: Although the amount of safety data in healthy volunteers is limited, the results raise no safety issues.***

## 8.5. Analysis of Submission-Specific Safety Issues

### 8.5.1. Hemorrhage

Hemorrhage was identified by the applicant as an AESI. The applicant reported the following results of their analyses on hemorrhage across studies (Module 5.3.5.3 Integrated Summary of Safety Section 4.6.2):

- For Pool A, hemorrhage events were less frequent in the defibrotide-treated subjects than in the historical controls (57% vs 75%).
- For Pool A, hemorrhage events occurred most commonly in the respiratory (23%) and gastrointestinal (21%) systems. The high rate of hemorrhage in the respiratory system was driven by epistaxis.
- For Pool A, the most common events reported were gastrointestinal hemorrhage (13%) and epistaxis (13%).
- For the subjects in Pool A treated with defibrotide 25 mg/kg/day, there was no difference between pediatric and adult subjects in the rate of hemorrhage (59% vs 57%).

Clinical Review

Tanya Wroblewski, M.D.

Donna Przepiorka, M.D. Ph.D.

NDA 208114

Defitelio (Defibrotide Sodium)

- For the subjects in Pool A treated with defibrotide 25 mg/kg/day, 16 (9%) had a fatal hemorrhage. The median duration of treatment with defibrotide in such subjects was 14 days (range, 1-39 days). Fatal hemorrhages were predominantly in the respiratory tract or central nervous system. Subjects who were ventilator-dependent or dialysis-dependent had a high rate of fatal hemorrhages.
- In Study 99-118, there was a higher rate of hemorrhage with 40 mg/kg/day than with 25 mg/kg/day (57% vs 49%). The difference by dose was especially true for gastrointestinal hemorrhage and in children.
- In Study 2006-05, 31% of the subjects had a report of hemorrhage, and the event was fatal for 4%.
- In Study 2004, the incidence of hemorrhage during the prophylaxis phase was similar for the defibrotide arm and the control arm (18% vs 14%, respectively). There was one fatal hemorrhage in each arm.

FDA assessed the risk of hemorrhage using the SMQNs Hemorrhage (excluding laboratory terms). The results are shown in Table 86.

**Table 86: Safety Population – Hemorrhage Events**

	SSP (n=176)		Other Defibrotide- Treated Patients (n=1648)		PK/PD Study Volunteers (n=70)	
SMQN Hemorrhages <sup>a</sup>	104	59%	384	23%	4 <sup>b</sup>	6%
SMQN Hemorrhages <sup>a</sup> Grade 3-5	62	35%	184	11%	0	
SMQN Hemorrhages <sup>a</sup> Related	43	24%	164	10%	0	
<u>Events by SOC in the SMQN Hemorrhages<sup>a</sup></u>						
Respiratory, thoracic and mediastinal disorders	45	26%	141	9%	0	
Gastrointestinal disorders	32	18%	146	9%	0	
Renal and urinary disorders	19	11%	53	3%	0	
Injury, poisoning and procedural complications	17	10%	17	1%	0	
Skin and subcutaneous tissue disorders	15	9%	17	1%	0	
Eye disorders	14	8%	14	1%	0	
Nervous system disorders	13	7%	19	1%	0	
Vascular disorders	12	7%	42	3%	0	
General disorders and administration site conditions	11	6%	16	1%	4 <sup>b</sup>	6%
Blood and lymphatic system disorders	7	4%	17	1%	0	
Reproductive system and breast disorders	4	2%	5	0%	0	
Cardiac disorders	1	1%	0	0%	0	
Ear and labyrinth disorders	1	1%	0	0%	0	
Investigations	1	1%	1	0%	0	
Hepatobiliary disorders	0	0%	1	0%	0	

Source: FDA analysis

<sup>a</sup> SMQN Hemorrhages (excluding laboratory terms)

<sup>b</sup> All events were at venipuncture or infusion sites.

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

FDA found that for the SSP, the most common (>20%) System Organ Class with hemorrhage terms was Respiratory, thoracic and mediastinal disorders (26%) (14% excluding epistaxis). The most common (>5%) Preferred Terms were epistaxis (14%), gastrointestinal hemorrhage (9%), hematuria (9%), pulmonary alveolar hemorrhage (9%), conjunctival hemorrhage (6%), catheter site hemorrhage (6%) and post procedural hemorrhage (6%). A grade 4-5 hemorrhage event was reported for 20%. FDA also confirmed the apparent relationship between defibrotide dose and bleeding risk (see Section 8.4.5.2).

To put the results of their analyses in context, the applicant noted that published studies showed that bleeding events were common after HSCT in general, severe or clinically significant bleeding occurred in 12% to 27%, and the risk of bleeding events was higher in patients with VOD (OR, 2.2; 95% CI, 1.4-3.6) (Gerber, Segal, et al. 2008; Nevo, Swan, et al. 1998; Pihusch, Salat, et al 2002). The applicant concluded that the risk of clinically severe hemorrhage in the subjects treated with defibrotide was comparable to the rates reported in the literature (Module 5.3.5.3 Integrated Summary of Safety Section 4.6.2)

There were also publications of 2 large (>1000 subjects per arm) randomized trials testing the efficacy of defibrotide (b) (4) 200 mg intravenously 4 times a day or 400 mg intravenously twice daily in comparison to heparin for thromboembolic prophylaxis through 7 days after surgical procedures. The incidences of bleeding reported in these studies were 0.3% vs 1.3%, respectively (Battistel, De Rosa, 1988) and 1.3% vs 1.4%, respectively (Gerosa, Calvani, et al. 1989).

**Reviewer Comments:**

- ***The known pharmacologic action of defibrotide and the dose-toxicity relationship for hemorrhage suggest the potential for bleeding due to defibrotide. I therefore agree with the applicant's proposal to include in the Prescribing Information a Warning & Precaution regarding this risk, instructions not to administer the drug in patients with overt bleeding, and instructions to withhold the drug prior to an invasive procedure.***
- ***I do not agree with the applicant's conclusion that the risk of bleeding in the intended population when treated with defibrotide was comparable to the rates reported in the literature. Since there was selective reporting of adverse events, there is a possibility that the actual event rates are higher. This question can only be addressed with a well-conducted randomized trial.***
- ***The data from the thromboembolic prophylaxis trials suggests that the bleeding risk with defibrotide using a lower dose (~11 mg/kg/day) is no greater than with heparin prophylaxis, but these data are not sufficient to address the risk in the intended population, and as such do not preclude the need for a randomized trial.***

### 8.5.2. Hypotension

The applicant also identified hypotension as an AESI. Richardson, et al. (1998) reported that transient mild hypotension occurred during infusion of defibrotide in 5 of 19 patients, and 2 patients in the series developed grades 3-4 hypotension, supporting the focus on hypotension as an adverse reaction. The applicant reported the following results of their analyses on hypotension across studies (Module 5.3.5.3 Integrated Summary of Safety Section 4.6.3:

- Fatal hypotension was reported for 2 subjects treated with defibrotide, and neither case was considered related to study drug.
- In Pool A, there was no dose-toxicity relationship for the TEAE hypotension (37% at defibrotide 25 mg/kg/day and 40% at defibrotide 40 mg/kg/day), and the historical control group had a higher incidence of the TEAE hypotension (50%) than subjects in the defibrotide-treated groups.
- The incidence of the TEAE hypotension was similar for adult (39%) and pediatric (34%) subjects using 25 mg/kg/day.
- The risk of hypotension during treatment with defibrotide was increased in subgroups where the risk of hypotension would be higher even without defibrotide (e.g., ventilator-dependent vs non-ventilator-dependent).
- In the prophylaxis study (Study 2004), the incidence of hypotension overall was minimal, and it occurred less in the study drug arm than in the controls (1% vs 2%).

(b) (4)

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

(b) (4)

***Reviewer Comment: At the present time, there is insufficient evidence to support the need for a Warning & Precaution in the Prescribing Information to address hypotension alone. It would be useful, however, to have objective data that can be verified, such as frequent blood pressure measurements in the peri-infusional period, to characterize the actual risk of hypotension in the intended population using the (b) (4) drug product.***

Clinical Review  
 Tanya Wroblewski, M.D.  
 Donna Przepiorka, M.D. Ph.D.  
 NDA 208114  
 Defitelio (Defibrotide Sodium)

### 8.5.3. Hypersensitivity Reactions

Based on class experience, FDA identified hypersensitivity events as a potential adverse reaction for defibrotide. The applicant identified hypersensitivity events in 5 defibrotide-treated subjects for which no other etiology was found; none of the cases was considered related to defibrotide. The applicant also identified a published case of anaphylaxis:

Artesani (2006) reported a 66 year-old woman who developed generalized urticaria, vomiting, fall in blood pressure and loss of consciousness within 15 min after defibrotide 200 mg intravenously. The symptoms resolved within 24 hours with supportive care. She had received and tolerated oral defibrotide 8 months earlier. Hypersensitivity was confirmed by skin tests performed by prick and by intradermal injection.

FDA assessed the risk of hypersensitivity using the SMQNs Hypersensitivity and Anaphylactic Reaction. The results are shown in Table 87.

**Table 87: Safety Population – Hypersensitivity Events**

	SSP (n=176)		Other Defibrotide- Treated Patients (n=1648)		PK/PD Study Volunteers (n=70)
<u>Hypersensitivity</u>					
SMQN Hypersensitivity	31	18%	88	5%	0
SMQN Hypersensitivity Grade 3-5	5	3%	20	1%	0
SMQN Hypersensitivity Related	2	1%	3	<1%	0
<u>Anaphylaxis</u>					
SMQN Anaphylactic Reaction	0		1	<1%	0
SMQN Anaphylactic Reaction Grade 3-5	0		1	<1%	0
SMQN Anaphylactic Reaction Related	0		0		0

Source: FDA analysis

Events in the SMQN Hypersensitivity were common (5% - 18%), but the events were considered related for only 2 (1%) subjects in the SSP and 3 (<1%) in the group of Other Defibrotide-Treated Patients. All events reported as related were rashes. No narratives for hypersensitivity reactions were submitted, so it was not possible to further characterize these events. There was one case in the SMQN Anaphylactic Reaction, and it was listed as unrelated to study drug. The SAE narrative for this case noted sepsis as the potential alternate etiology, but the text did not have sufficient information to assess this.

In addition to the one anaphylactic reaction described above, the other hypersensitivity reactions reported in the literature or postmarketing included rash, urticaria and angioedema. Additional data were available from publications of 3 large (>1000 subjects treated with defibrotide) trials testing the efficacy of defibrotide (b) (4) 200 mg

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

intravenously 4 times a day or 400 mg intravenously twice daily for thromboembolic prophylaxis through 7 days after surgical procedures. The incidences of allergic reactions in the defibrotide-treated subjects reported in these studies were 0.5% to 0.8% (Battistel, De Rosa, 1988; Ferrari, Cornelli, et al. 1988; Gerosa, Calvani, et al. 1989).

***Reviewer Comment: The data from the hepatic VOD safety population and the large clinical trials of defibrotide for thromboembolic prophylaxis after surgery support the conclusion that defibrotide may cause hypersensitivity reactions, but the incidence appears to be low. The published case of anaphylaxis, however, shows that life-threatening hypersensitivity reactions to defibrotide can occur. Therefore, I agree with the applicant's proposal to include in the Prescribing Information a contra-indication for patients with known hypersensitivity to defibrotide. In addition, the potential for anaphylaxis warrants a Warning & Precaution.***

## 8.6. Specific Safety Studies/Clinical Trials

There were no other special safety studies submitted for review.

## 8.7. Additional Safety Explorations

### 8.7.1. Human Carcinogenicity or Tumor Development

The applicant provided an assessment of relapse in patients in Pool A transplanted for malignancy. They calculated that in the defibrotide-treated subjects the incidence of recurrent malignancy reported as a TEAE was 4%, and the incidence of a malignant disease as a fatal TEAE was 5%. In the historical controls, the incidence of a malignant disease as a fatal TEAE was 3%. They concluded that defibrotide did not increase the risk of recurrent malignancy (Module 5.3.5.3 Integrated Summary of Safety Section 4.12.13).

***Reviewer Comment: Given the relatively short duration of treatment and follow-up, and the high background of early mortality, a meaningful assessment of development of new cancers was not possible.***

### 8.7.2. Human Reproduction and Pregnancy

There were no safety data submitted for patients who were pregnant or breast-feeding when treated with defibrotide.

### 8.7.3. Pediatrics and Assessment of Effects on Growth

There were no growth effects studies. See Section 8.4.7.1 for the discussion of safety in the pediatric population.

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

#### 8.7.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The applicant reported no cases of overdose of defibrotide (Module 5.3.5.3 Integrated Analysis of Safety Section 8.5). There is no established antidote for defibrotide, and it is not dialyzable.

Defibrotide does not have a known potential for dependence. Whether abrupt cessation of therapy with defibrotide would have an adverse effect on hemostasis was not studied.

#### 8.7.5. Drug-Drug Interactions

No formal drug-drug interaction studies were conducted by the applicant. They provided the following published reports to support their conclusion that “defibrotide may enhance the activity of antithrombotic/fibrinolytic drugs such as heparin or alteplase, but not anticoagulant drugs such as warfarin, apixaban and rivaroxaban” (Module 5.3.5.3 Integrated Summary of Safety Section 8.3):

- Fareed, Moorman, et al (2013) assessed the effect of defibrotide 50-250 mcg/mL on the activity of direct-acting anticoagulants and an antiplatelet agent ex vivo in human blood and platelet-rich plasma. They reported that defibrotide alone had no effect on agonist-induced platelet aggregation, and it did not alter the aggregation profiles of the other agents when tested in combination. Defibrotide itself did not prolong the activated clotting time (ACT), but it did augment the activity of dabigatran on ACT; the interactions with rivaroxaban and apixaban were weak in the ACT. Defibrotide had no effect in the thrombin generation assay, and it increased the activity of only dabigatran in that assay.
- Fareed, Hoppensteadt, et al (2013) assessed the effect of defibrotide 100 mcg/mL on the activity of anticoagulants on coagulation studies ex vivo in human blood and plasma. Defibrotide had no interactive effect on the PT for any of the agents (dabigatran, rivaroxaban, apixaban or plasma from warfarin-treated patients), but it did enhance the activity of dabigatran on the aPTT slightly.
- Hoppensteadt, Fareed, et al (2010) assessed the effect of defibrotide 12.5 – 100 mcg/mL on the activity of heparin ex vivo in human blood. They reported that defibrotide did not prolong the ACT by itself or with low molecular weight heparin (LMWH), but it did increase the effect of unfractionated heparin (UFH) on ACT. Interactive effects in the thrombin generation assay were seen with both types of heparin. Additionally, defibrotide alone did not prolong the aPTT, but the aPTT of heparinized plasma was increased by defibrotide.
- Paul, Gresele, et al (1993) assessed the effect of defibrotide in a murine model of thrombin-induced thromboembolism. Pretreatment with defibrotide inhibited the fatal effects of thrombin infusion in this model. The effect of defibrotide was abolished by concurrent administration of tranexamic acid and was unaffected by aspirin. The effect of defibrotide in this model was enhanced by recombinant tPA and by UFH.

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

- Porta, Pescador, et al (1990) assessed the effect of defibrotide 10 or 50 mg/kg intravenously on the activity of heparin (Calciparina, Italfarmaco) on coagulation tests in rabbits. Defibrotide alone had a very minimal effect on thrombin time, and neither dose altered the aPTT significantly. The effect of heparin on thrombin time was enhanced at both dose levels of defibrotide, but there was no interactive effect on aPTT.
- Pogliani, Salvatore, et al (1989) assessed the effect of defibrotide 400 mg intravenously on the activity of heparin 2500 IU intravenously on coagulation assays in healthy volunteers. The effect of defibrotide alone was not tested. Comparing results at 2 hours after infusion, the aPTT was prolonged with the combination to a greater extent than with heparin alone, but there was no interactive effect on the PT or on the concentrations of heparin, antithrombin III, tPA or PAI.

**Reviewer Comments:**

- ***Based on the effects of defibrotide on the activity of other anticoagulants in coagulation assays, I agree with the applicant that there is a potential for direct interaction with UFH, LMWH, dabigatran and fibrinolytic agents. However, since defibrotide may cause bleeding when used alone based on the observed pharmacologic actions, there may also be additive effects on the risk of clinical hemorrhage when defibrotide is given concurrently with any anticoagulant. I therefore agree with the applicant's proposal to contra-indicate concurrent use with any anticoagulant or fibrinolytic agent.***
- ***The finding that tranexamic acid abolished the protective effect on defibrotide in a murine model of thromboembolism is of interest, but there is no clinical information on this interaction to confirm the effect.***

## 8.8. Safety in the Postmarket Setting

### 8.8.1. Safety Concerns Identified Through Postmarket Experience

The applicant has marketing authorization for defibrotide as Defitelio for treatment of severe hepatic VOD following HSCT in the EU since 2013 and in Israel since 2015. The applicant estimated that 436 patients were exposed to commercial defibrotide from the date of initial authorization 10/18/2013 through the end of the last reporting period 4/18/2015 (Defibrotide Periodic Safety Update Report dated 6/24/2015). They indicated receipt of six serious adverse event reports in the postmarketing period. These included five events of bleeding or coagulopathy.

The applicant was also required by the EMA to develop a registry of patients with severe hepatic VOD following HSCT to investigate long-term safety, health outcomes and patterns of

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

utilization of defibrotide (Defibrotide Periodic Safety Update Report dated 6/24/2015). There are no interim reports available to date from this registry.

From 1986 through 2009, defibrotide drug substance was marketed in Italy as Prociclide or Noravid for oral or systemic use for prophylaxis of deep vein thrombosis and for treatment of thrombophlebitis (Module 5.3.5.3 Integrated Summary of Safety Section 1). The applicant provided the periodic safety update reports for 1995-1999, 2000-2005 and 2005-2008. The reports contained interval rather than cumulative summaries of information. During the period of 1995-2008, [REDACTED] (b) (4). The applicant estimated that 35,000 patients were exposed during the 2000-2005 interval. There were two unexpected serious adverse events identified from the postmarketing experience. These were one case of angioedema and urticaria during the 2005-2008 period and one case of hospitalization for pyrexia during the 1995-1999 period. There was also one case of an allergic reaction identified in a literature review (see Section 8.5.3).

Using Empirica Signal to review reports in FAERS, this reviewer found a signal for toxic epidermal necrolysis (TEN) for defibrotide. There were two cases of TEN identified, and both occurred in patients who had undergone allogeneic HSCT. Both patients were also taking multiple other drugs at the time, so it was not possible to confirm a causal relationship of the TEN with defibrotide.

***Reviewer Comment: There are no new unexpected safety events emerging from the review of the postmarketing experience. In fact, given the extensive use of the various marketed formulations of defibrotide, the review is most remarkable for the very low number of suspected unexpected serious adverse reactions reported.***

## 8.9. Additional Safety Issues

### 8.9.1. Safety Issues From Other Disciplines

See Section 8.1.3 for a discussion of relevant issues identified by reviewers from other disciplines.

### 8.9.2. Safety Information for Other Sources

#### 8.9.2.1. The DF-VOD Trial

The applicant submitted a trial report for the protocol "Defibrotide For The Treatment Of Hepatic Venous Occlusive Disease After Stem Cell Transplantation (DF-VOD TRIAL)" dated 2/24/2011 and signed by Tiziano Barbui and Gianni Tognoni. The provenance of the report was not described, and the documentation to support the integrity of the data was not provided (Module 5.3.5.3 Integrated Summary of Safety Page 25).

## Clinical Review

Tanya Wroblewski, M.D.

Donna Przepiorka, M.D. Ph.D.

NDA 208114

Defitelio (Defibrotide Sodium)

The DF-VOD Trial was a multi-center, open-label, randomized, controlled trial comparing defibrotide 40 mg/kg/day (10 mg/kg iv every 6 hours) to supportive care for treatment of patients after HSCT with a clinical diagnosis of hepatic VOD by the Baltimore criteria, biopsy-proved hepatic VOD, or hemodynamically-proven hepatic VOD. Treatment with defibrotide was to be administered for at least 14 days. The stated primary objective of the study was to the efficacy of defibrotide on the survival of patients with VOD. The primary endpoints of the trial were VOD complete remission and mortality at study day 100 in the ITT population. The target accrual was 340 subjects.

Study subjects were followed according to institutional standards. The planned duration of follow-up was 100 days. Criteria for assessing safety included non-fatal major bleeding (any bleeding requiring transfusion of at least 2 blood units or requiring surgery), minor bleeding (any bleeding which does not meet the definition for major bleeding), SAEs and any adverse reaction causing treatment withdrawal. SAEs were not recorded if they were expected signs or symptoms of VOD, expected events in the HSCT recovery period, or study endpoints. Events were coded according to MedDRA version 13.0 and graded according to NCI CTCAE version 3.0.

The study was conducted September, 2001, through October, 2005. The trial was terminated early due to slow accrual. At the time of the analysis, 68 subjects were enrolled (34 on each arm) at 19 centers in Europe and Israel. The defibrotide and control arms were similar with regard to median age, HSCT type (allogeneic vs not allogeneic), concurrent pulmonary dysfunction, and concurrent renal dysfunction, but the defibrotide arm had a higher proportion of males (68% vs 47%), a higher proportion with VOD diagnosed  $\leq 15$  days from HSCT (79% vs 68%), fewer subjects with concurrent organ dysfunction of any type (47% vs 59%), and a lower median bilirubin (4.3 vs 6.3 mg/dL). Only 15% of the subjects were  $\leq 20$  years old, and they were evenly distributed between the study arms.

Mean follow-up was 47 days on the defibrotide arm vs 51 days on the control arm. On the defibrotide arm, the study subject received a mean of 11 days (SD, 10 days) of treatment. Only 12 subjects (35%) received the minimum required 14 days of therapy. The reasons for early discontinuation included death (9), non-fatal bleeding (8), GvHD (1), renal insufficiency (1), and VOD absent on biopsy (1). Data were not submitted for 2 subjects.

In the comparative assessment of safety outcomes, the incidences were similar for the defibrotide arm and the control arm for deaths (62% vs 59%), SAEs (68% for each arm), grade 4-5 SAE (74% vs 62%), non-fatal bleeding events (41% vs 44%), and major bleeding events (32% vs 27%). There were no SAEs considered related to defibrotide. For subjects with VOD and MOF, death within 14 days of randomization occurred in 9/16 (56%) on defibrotide vs 9/20 (45%) on the control arm. The authors concluded that defibrotide was well-tolerated, and there were no safety concerns.

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

**Reviewer Comment: The 25% rate of discontinuations for nonfatal bleeding in the defibrotide arm in the DF-VOD Trial using the 40 mg/kg/day dose is higher than reported for the SSP (13%) using the 25 mg/kg/day dose. Although the number of subjects in the DF-VOD Trial is small, the trend is consistent with a relationship between dose and risk of bleeding.**

#### 8.9.2.2. Literature Review

The applicant identified 713 articles and abstracts in the available literature published during the period January, 1998 – April 2014 using the search terms “Defibrotide,” including Defitelio®, Prociclide®, Noravid®, and Denelasi®. They provided a summary tabulation of 44 clinical studies or reports that included comments on safety or tolerance of defibrotide in the setting of prevention or treatment of VOD (Module 5.3.5.3 Integrated Summary of Safety Appendix 2). The principle adverse event identified in the literature review was hemorrhage.

FDA reviewed each of the identified publications. The only new potential safety concern came from the report of Bulley, Strahm, et al. (2007) in which they indicated that defibrotide (dose either 29 or 40 mg/kg/day) was discontinued in one patient who developed facial palsy and increased rigidity while being treated for hepatic VOD after HSCT. This patient did not have an intracranial hemorrhage. The clinical course after discontinuation of defibrotide was not described.

**Reviewer Comments: The report of potential neurological toxicity is unique, but a single case in the absence of biological plausibility and lack of description of the clinical course upon dechallenge is not persuasive. Overall, the literature review revealed no new safety concerns.**

#### 8.9.2.3. Studies in Other Indications

The applicant emphasized that their integrated summary of safety submitted was focused on the intended population, patients with hepatic VOD and MOF after HSCT, and that supporting safety data would be limited to studies in patients with related indications (Module 5.3.5.3 Integrated Summary of Safety Section 2.1). The high background rate of adverse events in the HSCT population confounds the analysis of adverse reactions, so FDA requested additional information on safety of defibrotide in populations with fewer co-morbidities. The following information was made available for review:

- The Defibrotide Investigator’s Brochure summarized the adverse drug reactions identified in clinical studies or literature reports through 12/31/2013. Among the 9,826 patients with peripheral occlusive arterial disease, thrombophlebitis, deep vein thrombosis or other disorders not hepatic VOD, 146 (1.5%) had a reported adverse drug reaction. The most

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

common adverse drug reactions (>0.1%) were rash (0.25%), hemorrhage (0.24%), incision site hemorrhage (0.17%), pruritus (0.16%), dyspepsia (0.13%), headache (0.13%), and nausea (0.12%) (Investigator's Brochure dated 3/12/2014 Table 32). The dose and route of defibrotide related to these adverse drug reactions was not reported.

- An undated report of a study by "Professor L. Scullica" sponsored by Crinos, S.P.A. indicated that there were no side effects noted for 53 adults with retinal venous or arterial thrombosis treated with (b) (4) defibrotide drug product using doses of 200 – 400 mg intramuscularly on day 1 followed by 200 mg intramuscularly daily for an additional 14 days to 3 months (Response to Information Request received 12/9/2015).
- An undated report of a study by "Professor G. Guagiano" sponsored by Crinos, S.P.A. indicated that there were no clinical side effects nor effects on hematopoietic, renal or hepatic function noted for 30 adults with peripheral venous or arterial thrombosis treated with pre-1995 defibrotide drug product using doses of 400 mg intravenously on day 1 followed by 200 mg intramuscularly daily for up to an additional 14 days (Response to Information Request received 12/9/2015).
- The applicant provided a summary tabulation of 52 randomized trials published 1986 to 2000 that evaluated defibrotide for the prevention or treatment of deep vein thrombosis, treatment of peripheral arterial disease, prevention or treatment of vascular access thrombosis, or other indications (not hepatic VOD). Seventeen of these trials were placebo-controlled. There were no unexpected adverse events reported (Response to Information Request received 11/6/2015). The series included 2 large (>1000 subjects) trials testing the efficacy of defibrotide 200 mg intravenously 4 times a day for thromboembolic prophylaxis after surgical procedures. The incidences of adverse reactions reported in these studies were <1% and 1.3% (Ferrari, Cornelli, et al. 1988; Battistel, De Rosa, 1988).

**Reviewer Comment: The results presented, especially in the very large trials using the (b) (4) defibrotide drug product, shows a very low incidence of adverse reactions when defibrotide is used short term for prevention or treatment of thromboembolic events. This low incidence of adverse reactions is consistent with the postmarketing data.**

### 8.9.3. 120-Day Safety Update

There was no additional information in the 120-day safety update for Study 2005-01 or Study 99-118. The sponsor did provide additional information from the expanded access protocol (Study 2006-05). The update include patients enrolled through 4/18/2015 with a data cut-off of 9/30/2015. The analysis included a total of 606 patients with hepatic VOD and MOF treated with defibrotide 6.25 mg/kg every 6 hours pooled from 2006-05 (n=430), 2005-01 (n=102) and 99-117 (n=74). There were no new safety issues identified in the updated pooled analysis.

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

Derivation of adverse reactions is complicated by the lack of a control arm for comparison of incidences, and therefore adverse reactions will be based on TEAE without regard to causality (excluding veno-occlusive disease). Table 88 shows the updated tabulation of common adverse reactions and common grades 4-5 adverse reactions reported in the SSP.

**Table 88: SSP – Common Adverse Reactions**

Preferred Term	Any Grade (n=176)		Grade 4-5 (n=176)	
Hypotension	65	37%	12	7%
Diarrhea	43	24%	0	0%
Multi-organ failure	38	22%	38	22%
Vomiting	31	18%	0	0%
Renal failure	29	16%	13	7%
Nausea	28	16%	0	0%
Epistaxis	24	14%	0	0%
Respiratory failure	20	11%	17	10%
Hypertension	17	10%	1	1%
Hypoxia	17	10%	10	6%
Pyrexia	17	10%	1	1%
Gastrointestinal hemorrhage	15	9%	5	3%
Pulmonary alveolar hemorrhage	15	9%	12	7%
Sepsis	12	7%	9	5%
Graft versus host disease	11	6%	7	4%
Lung infiltration	10	6%	5	3%
Pneumonia	9	5%	4	2%
Pulmonary hemorrhage	7	4%	4	2%
Infection	6	3%	3	2%
Hemorrhage intracranial	5	3%	4	2%
Hyperuricemia	4	2%	4	2%
Cerebral hemorrhage	3	2%	3	2%

Source: FDA analysis

**Reviewer Comment: The results in the 120-day safety update raise no new safety concerns.**

## 8.10. Integrated Assessment of Safety

The safety information was reviewed for 1894 individuals exposed to defibrotide in seven sponsored studies or trials of treatment of VOD, treatment of other disorders, prevention of VOD, or evaluations of PK and PD. One QT study was conducted in healthy volunteers. This safety information was supplemented by a retrospective registry study, available published literature, legacy clinical study reports, and postmarketing information for all formulations of defibrotide. The doses of defibrotide in this summary are stated as defibrotide salt as identified in the individual protocols.

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

The types of safety data recorded (deaths, serious adverse events, adverse events of interest, common adverse events, adverse event characterization, common laboratory tests and vital signs) varied by protocol. None of the trials in patients with VOD collected all treatment-emergent adverse events. The best available adverse event information to assess safety of the proposed dose in the intended population was pooled data from 176 subjects with hepatic VOD and MOF after HSCT treated with defibrotide 6.25 mg/kg intravenously every 6 hours (total 25 mg/kg/day) in Studies 2005-01 and 99-118. This group is called the Selected Safety Population (SSP).

There were 105 males and 71 females with hepatic VOD and MOF after HSCT in the SSP. The median age was 25 years (range, 0.1-72 years). Pediatric patients comprised 37%, and there was a single subject  $\geq 65$  years old. Twenty-four percent of the subjects were ventilator- or dialysis-dependent. The subjects were treated with defibrotide for a median of 21 days (range, 1-83 days). The results of *analyses in the SSP pool* showed:

- Mortality within 30 days of the last dose of defibrotide was 55%. The most common fatal adverse events were multi-organ failure (22%), respiratory failure (7%), pulmonary alveolar hemorrhage (4%), sepsis (4%), graft versus host disease (3%), renal failure (3%), pneumonia (2%), hepatic failure (2%) and hypoxia (2%). There were no deaths that could be clearly ascribed to defibrotide.
- The most common ( $\geq 10\%$ ) SAEs were multi-organ failure, hypotension, respiratory failure and renal failure (Table 70). The most common ( $\geq 1\%$ ) TEAEs resulting in treatment discontinuation were pulmonary alveolar hemorrhage, hypotension, multi-organ failure, catheter site hemorrhage, pulmonary hemorrhage, cerebral hemorrhage and sepsis (Table 71). SMQN Hemorrhage events resulted in discontinuation for 13% of the subjects.
- The most common ( $\geq 10\%$ ) TEAEs were hypotension, diarrhea, multi-organ failure, vomiting, renal failure, nausea, epistaxis, respiratory failure, hypertension, hypoxia and pyrexia (Table 72). The most common ( $>5\%$ ) grade 4-5 TEAE were multi-organ failure, respiratory failure, renal failure, hypotension, pulmonary alveolar hemorrhage and hypoxia.
- A grade  $\geq 3$  elevation was reported in 93% for bilirubin and in 27% for creatinine. In addition, 25% had a grade  $\geq 3$  elevation in aPTT, but the elevation of aPTT was not consistent over time with defibrotide use, and there was no dose-dependent increase in aPTT in Study 99-118.

In general, the analyses of the SSP revealed no unexpected events for patients with VOD after HSCT.

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

The clinically significant observations made by the applicant in comparative analyses included:

- In Study 2005-01, fatal hemorrhages were more frequent in the treatment group than in the historical controls (15% vs 6%), but the control group had a higher rate of fatal TEAE overall (section 8.4.1).
- The TEAE incidence was at least 5% higher in the treatment group than in the control group for the TEAEs multi-organ failure, decubitus ulcer, catheter site hemorrhage, headache and pulmonary hemorrhage in Study 2005-01, and for respiratory failure during the prophylaxis phase of Study 2004 (Section 8.4.5.1).
- There were no important differences between study groups for changes in renal or hepatic function on Study 2005-01. In the prophylaxis phase of Study 2004, more subjects in the defibrotide arm has a shift to bilirubin >10 mg/mL than in the control arm, but a similar difference in shift to an extreme bilirubin was not observed in Study 2005-01. (Section 8.4.6.1)
- There was no adverse impact of defibrotide use on time to hematopoietic recovery or the incidence of graft failure in Study 2005-01 or in the prophylaxis phase of Study 2004 (Section 8.4.6.1).
- The outlier analysis of vital signs in Study 2005-01 showed no differences between the study groups for low systolic or low diastolic blood pressure (Section 8.4.6.2). (It should be noted that these vital sign measurements did not necessarily coincide with defibrotide infusion).
- In the QT study, no safety signal was identified on the basis of central tendency, outlier analysis, or exposure effect modeling (Section 8.4.6.3).

Overall, there were no substantial and consistent adverse effects of defibrotide when used as treatment or prevention of VOD in the HSCT recipients in comparison to safety outcomes in the respective control groups as assessed by the applicant. In support of a conclusion that defibrotide is safe, in two large (>1000 subjects) trials testing the efficacy of defibrotide 200 mg (b) (4) intravenously 4 times a day for thromboembolic prophylaxis after surgical procedures, the incidences of adverse reactions reported were low (<1% and 1.3%) (Section 8.9.2.3).

**Hemorrhage** is a clear potential serious adverse reaction for defibrotide based on its pharmacologic effects and the apparent dose-toxicity relationship (Section 8.4.5.2). In the SSP, events in the SMQN Hemorrhages (excluding laboratory terms) occurred in 59% of subjects, and the events were grade 4-5 for 20%. The most common Preferred Terms for hemorrhage were epistaxis (14%), gastrointestinal hemorrhage (9%), hematuria (9%), and pulmonary alveolar hemorrhage (9%). The applicant noted that these event rates were comparable to

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

those reported in the literature, and that by their analysis, hemorrhage events were less frequent on the defibrotide arm than on the control arm in Study 2005-01, suggesting that the proposed dose of 6.25 mg/kg every 6 hours is tolerable in this population. To ensure that safe use can be recapitulated in practice, the Prescribing Information should contain at least the same levels of controls as the protocols with regard to warnings, patient selection, monitoring, and treatment interruption for bleeding or invasive procedures.

**Hypersensitivity** is a second potential serious adverse reaction for defibrotide (Section 8.5.3). There were no immunogenicity studies performed. On analysis of clinical outcomes, events in the SMQN Hypersensitivity that were listed as related occurred in 1% of subjects in the SSP and <1% in Other Defibrotide-Treated Patients in the safety population. The majority of these events were types of rash, but further characterization was not possible due to the lack of narrative for these events. In three large (>1000 subjects treated with defibrotide) trials testing the efficacy of defibrotide (pre-1995 product) 200 mg intravenously 4 times a day or 400 mg intravenously twice daily for thromboembolic prophylaxis through 7 days after surgical procedures, the incidences of allergic reactions in the defibrotide-treated subjects were 0.5% to 0.8%. There was also one published case report of anaphylaxis after intravenous infusion of 200 mg of defibrotide, and hypersensitivity in this case was confirmed later by skin test. Although the incidence of hypersensitivity reactions is low, the occurrence of anaphylaxis warrants a warning in the Prescribing Information.

In the assessment of safety in **special populations**, there was an inverse trend for pulmonary hemorrhage with age for the subjects in the VOD treatment trials, but this trend was not confirmed in the prophylaxis phase of the VOD prevention trial (Section 8.4.7.2). There was not a sufficient number of geriatric subjects in the safety database to allow for a meaningful analysis in this subgroup. There was a higher incidence of hemorrhage events and hypotension during defibrotide treatment in patients who were dialysis- or ventilator-dependent, but this could not be ascribed to defibrotide specifically, since the same trend was seen in the control group in Study 2005-01.

No formal **drug-drug interaction** studies were conducted by the applicant. Reports from the published literature showed that defibrotide enhanced the activity of dabigatran, UFH or LMWH ex vivo in human blood or plasma and in one clinical study in healthy volunteers (Section 8.7.5). The pharmacologic activity of defibrotide suggests that it might also be expected to enhance the activity of fibrinolytic agents. The increased risk of bleeding due to these effects of defibrotide contra-indicate concurrent use with anticoagulants and fibrinolytic therapies. In a murine model of induced thromboembolism, tranexamic acid counteracted the protective effect of defibrotide. Although this interaction is biologically plausible, there are no confirmatory clinical data.

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

There were no additional unexpected serious adverse events reported in the ***postmarket setting*** since the approval of defibrotide in Europe in 2013 for treatment of severe hepatic VOD following HSCT. The majority of the related serious adverse events reported were involved bleeding or coagulopathy. There were similarly few related unexpected serious adverse events recorded in the periodic safety updates for the years 1995-2008 for the other formulations of defibrotide marketed in Italy.

***In summary***, there was a high rate of adverse reactions in the patients being treated for hepatic VOD with MOF using the proposed dose-schedule of defibrotide, but there was no consistent signal that any of the events was caused specifically by defibrotide. The published reports of safety of defibrotide in other populations and the review of the postmarket reports are consistent with the relative tolerability of defibrotide in the VOD trials. Hemorrhage, hypersensitivity and pharmacologic interaction with anticoagulants and fibrinolytic therapies are serious safety concerns, but these can be mitigated by appropriate warnings, contra-indications and instructions for patient selection and dose modifications in the Prescribing Information. The lack of complete safety data from a well-conducted randomized trial is a substantial deficiency that raises questions about the accuracy of the safety profile in the intended population as currently established, and this residual concern needs to be considered when weighing the overall risks and clinical benefits of this therapy.

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

## 9 Advisory Committee Meeting and Other External Consultations

---

There was no Advisory Committee meeting for defibrotide because the application did not raise significant public health questions regarding the role of defibrotide for this indication, and outside expertise was not necessary as there were no controversial issues that could benefit from an Advisory Committee discussion.

## 10 Labeling Recommendations

---

### 10.1. Prescribing Information

These recommendations for major changes to the clinically relevant aspects of the Applicant's proposed prescribing information are based on assessment of the label at the time this review was completed.

- INDICATIONS AND USAGE
  - Added "pediatric": Defitelio is indicated for the treatment of adult and pediatric patients with hepatic veno-occlusive disease also known as sinusoidal obstruction syndrome(SOS) with (b) (4) renal (b) (4) pulmonary dysfunction following hematopoietic stem cell transplantation

*Reviewer Comment: Pediatric population added. (b) (4) changed to more specific organ dysfunction of renal and pulmonary dysfunction.*

- DOSAGE AND ADMINISTRATION

- (b) (4)
- The label will not include (b) (4)

*Reviewer Comment: Due to the (b) (4)*

○ (b) (4)

- WARNINGS AND PRECAUTIONS

- Removed (b) (4)
- Removed (b) (4)

*Reviewer Comment: (b) (4)*

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

- Removed [REDACTED] (b) (4)

*Reviewer Comment: There was no data to suggest that defibrotide causes hypotension.*

- ADVERSE REACTIONS
- DRUG INTERACTIONS
- USE IN SPECIFIC POPULATION
  - Changes consistent with the Pregnancy and Lactation Labeling Rule
  - Removed [REDACTED] (b) (4)

*Reviewer Comment: The pediatric section should contain [REDACTED] (b) (4)*

- CLINICAL STUDIES
  - Due to the [REDACTED] (b) (4) will not be included in the prescribing information. [REDACTED] (b) (4)
  - Only descriptive statistics will be used for primary endpoint.

*Reviewer Comment: Due to [REDACTED] (b) (4)*

*cannot be included in the label.* [REDACTED] (b) (4)

## 10.2. Patient Labeling

This subsection is not applicable as defibrotide is administered intravenously to patients in a hospital under supervision.

## 10.3. Nonprescription Labeling

This subsection is not applicable for this review, as defibrotide will require a prescription.

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

## **11 Risk Evaluation and Mitigation Strategies (REMS)**

---

Given the safety profile of this drug, there are no additional risk management strategies required beyond the recommended labeling. Therefore the subsequent sections are not applicable for this review and have been omitted. Review of the Application and of the findings from the review teams, the Division of Risk Management in the Office of Surveillance and Epidemiology agree that a REMS is not needed to ensure the benefits of defibrotide exceed its risk.

## **12 Postmarketing Requirements and Commitments**

---

PMC #1 Description: Develop sensitive and specific anti-drug (defibrotide) binding and neutralizing assays. Submit Validation reports on the assays in a final report to the NDA.

PMC #2 Description: Evaluate patient's sera for binding and neutralizing antibodies to defibrotide using the validated assays from PMC 1 and submit the data in a final immunogenicity study report.

PMR #1 Description: Conduct an analysis of safety in a randomized, open-label multi-center clinical trial comparing defibrotide versus best supportive care in the prevention of hepatic VOD in adult and pediatric patients, including all adverse events, laboratory abnormalities and frequent peri-infusion vital signs.

## **13 Appendices**

---

### **13.1. References**

Artesani MC. 2006 Anaphylactic shock to defibrotide. *Allergy* 61:1022.

Battistel V, De Rosa A. 1988 Comparative study of defibrotide and calcium heparin in the prevention of postoperative deep venous thrombosis. A randomized multicenter study. *Minerva Medica* 79: 783-790.

Bras G, Jeliffe DB, Stuart KL, et al. 1954 Venous-occlusive disease of the liver with non-portal type of cirrhosis occurring in Jamaica. *Arch Pathol* 57:285-300.

Clinical Review

Tanya Wroblewski, M.D.

Donna Przepiorka, M.D. Ph.D.

NDA 208114

Defitelio (Defibrotide Sodium)

Bearman SI. 1995 The syndrome of hepatic veno-occlusive disease after marrow transplantation. *Blood* 85:3005-3020

Bearman SI, Garnet L, Motomi M, et al. 1993. Veno-occlusive disease of the liver: development of a model for predicting fatal outcome after marrow transplantation. *JCO* 9: 1729-1736.

Bearman SI. 2000. Veno-occlusive disease of the liver. *Curr Opin in Onc* 12:103-109.

Bulley SR, Strahm B, Doyle J, Dupuis LL. 2007 Defibrotide for the treatment of hepatic veno-occlusive disease in children. *Pediatr Blood Cancer* 48:700–704.

Carreras E, Hartmut B, Arcese, W, Vernant, JP, Tomas JF, et al. 1998 Incidence and outcome of hepatic veno-occlusive disease after blood or marrow transplantation: A prospective cohort study of the european group for blood and marrow transplantation. *Blood* 92: 3599-3604.

Carreras E, Viguria MC, Rovira M, et al. 1998 Veno-occlusive disease of the liver after allogeneic blood and marrow transplantation: A retrospective analysis of 376 consecutive BMT performed in a single center. *Bone Marrow Transplant* 21(suppl 1): S239.

Carreras E, Diaz-Ricart M. 2001 The role of the endothelium in the short-term complications of hematopoietic SCT. *Bone Marrow Transplant* 46: 1495-1502.

Carreras E, Diaz-Beya M, Rosinol L, Martinez C, et al. 2011 The Incidence of veno-occlusive disease following allogeneic hematopoietic stem cell transplantation has diminished and the outcome improved over the last decade. *Biol Blood Marrow transplant* 17: 1698-1720.

Coppell JA, Richardson PG, Soiffer R, Martin PL, Kernan NA, Chen A, Guinan E, Vogelsang G, et al. 2012 Hepatic Veno-occlusive disease following stem cell transplantation: incidence clinical course, and outcome. *Biol. Blood Marrow Transplant* 16: 157-168

Corbacioglu S, Greil J, Peters C, Wulffraat N, et al. 2004 Defibrotide in the treatment of children with veno-occlusive disease (VOD): a retrospective multicenter study demonstrates therapeutic efficacy upon early intervention. *Bone Marrow Transplant* 33: 189-195

Corbacioglu S, Cesaro S, Farac, et al. 2012 Defibrotide for prophylaxis of hepatic veno-occlusive disease in pediatric haemopoietic stem-cell transplantation: an open-label, phase 3 randomized controlled trial. *Lancet* 379: 1301-1309.

## Clinical Review

Tanya Wroblewski, M.D.

Donna Przepiorka, M.D. Ph.D.

NDA 208114

Defitelio (Defibrotide Sodium)

Cutler, C, Stevenson K, Haesso TK, Richardson PG, et al. 2008 Sirolimus is associated with veno-occlusive disease of the liver after myeloablative allogeneic stem cell transplantation. *Blood* 112: 4425-4431.

Dignan FI, Wynn RF, Hazic N, Karani J, et al. 2013 BCSH/BSHMT guideline: diagnosis and management of veno-occlusive disease (sinusoidal obstruction syndrome) following hematopoietic stem cell transplantation. *Brit J. Hematology* 163; 444-457.

DeLeve L. 1998 Glutathione defense in non-parenchymal cells. *Sem Liver Dis* 18: 403-413.

DeLeve L, Shulman H, McDonald G. 2002 Toxic Injury to Hepatic Sinusoids: Sinusoidal obstruction syndrome (veno-occlusive disease). *Sem In Liver Disease* 1: 27-41.

Essell JH, Schoreder MT, Harman GS, et al. 1998 Ursodiol prophylaxis against hepatic complications of allogeneic bone marrow transplantation. A randomized double-blind, placebo-controlled trial. *Ann Intern Med* 128: 975-981.

Ferrari P, Cornelli U, Dina F, et al. 1988 Defibrotide in the prophylaxis of deep venous thromboses in general surgery: preliminary results of a multicenter study. *Minerva Medica* 79: 551-561.

Gerber DE, Segal JB, Levy MY, Kane J, Jones RJ, Streiff MB. 2008 The incidence of and risk factors for venous thromboembolism (VTE) and bleeding among 1514 patients undergoing hematopoietic stem cell transplantation: implications for VTE prevention. *Blood* 112: 504-10.

Gerosa C, Calvani A, Cornelli U, et al. 1989 A multicenter study of defibrotide in the prevention of deep venous thrombosis. Final results. *Minerva Chir* 44: 1507-1516.

Jones RJ, Lee KSK, Beschorner W, Vogel VG, et al. 1987 Veno-occlusive Disease of the Liver Following Bone Marrow Transplantation. *44: 778-783.*

Hasegawa S, Horive K, Kawabe T, et al. 1998 Veno-occlusive disease of the liver after allogeneic bone marrow transplantation in children with hematologic malignancies: incidence, onset time and risk factors. *Bone Marrow Transplant* 22: 1191-1197.

Maximova N, Pizzol A, Giurici N, Granzotto M. 2015 Does defibrotide induce a delay to polymorphonuclear neutrophil engraftment after hematopoietic stem cell transplantation? Observation in a pediatric population. *Adv Ther* 32:381-6.

## Clinical Review

Tanya Wroblewski, M.D.

Donna Przepiorka, M.D. Ph.D.

NDA 208114

Defitelio (Defibrotide Sodium)

McDonald GB, Hinds MS, Fisher LD, et al. 1993 Veno-occlusive disease of the liver and multi-organ failure after bone marrow transplantations: a cohort study of 355 patients. *Ann Intern Med* 118:255-267.

McDonald GB, Sharm P, Matthews De, et al. 1984 Veno-occlusive disease of the liver after bone marrow transplantation: diagnosis, incidence and predisposing factors. *Hepatology* 4: 116-122.

Nevo S, Swan V, Enger C, et al. 1998 Acute bleeding after bone marrow transplantation (BMT) - incidence and effect on survival. A quantitative analysis in 1,402 patients. *Blood* 91:1469-77.

Pihusch R, Salat C, Schmidt E, et al. 2002 Hemostatic complications in bone marrow transplantation: a retrospective analysis of 447 patients. *Transplantation* 74:1303-9.

Richardson P, Gunman E. 1999 The pathology diagnosis and treatment of hepatic veno-occlusive disease: current status and novel approaches. *Br. J. Haematol* 107: 485-493.

Richardson PG, Elias AD, Krishan A, et al. 1998 Treatment of severe veno-occlusive disease with defibrotide: compassionate use results in response without significant toxicity in a high-risk population. *Blood* 92: 737-744.

Richardson PG, Soiffer RG, Antin JH, et al. 2010 Defibrotide for the treatment of severe hepatic veno-occlusive disease and multi-organ failure after stem cell transplantation: A multicenter, randomized ,dose finding trial. *Biol Blood Marrow Transplant* 16: 1005-1018

Salat C, Holler E, Kolb HJ, et al. 1999 The relevance of plasminogen activator inhibitor (PAI-1) as a maker for the diagnosis of hepatic veno-occlusive disease in patients after bone marrow transplantation. *Leuk Lymphoma* 33: 25-32.

Schots RM, Kaufman L, Van Riet I, et al. 1998. Monitoring of C-reactive proteins after allogeneic bone marrow transplantation identified patents at risk of severe transplant-related complications and mortality. *Bone Marrow Transplant* 22: 79-85.

Shulman HM, Fisher LD, Schoch HG, et al. 1994 Veno-occlusive disease of the liver after marrow transplantation: histological correlates of clinical signs and symptoms. *Hepatology* 19: 1171-1181.

Triplett BM, Kuttub HI, Kang G and Leung W. 2015 Escalation to High-Dose Defibrotide in Patients with Hepatic Veno-Occlusive Disease. *Biol Blood Marrow Transplant* 21:2148-53.

Clinical Review  
Tanya Wroblewski, M.D.  
Donna Przepiorka, M.D. Ph.D.  
NDA 208114  
Defitelio (Defibrotide Sodium)

### 13.2. Financial Disclosure

The covered studies submitted by the applicant include Study 2005-01, Study 2004-000592-33, Study 2006-05 and Study R09-1425.

Study 2004 ended in 2009 and additional data was collected and verified at the request of FDA in 2011 and 2012. Attempts were made to collect financial disclosure from all investigators. Despite best efforts from the Sponsor, information was not obtained for all investigators.

Study 2006-05 collected financial disclosure information at the start of the study in 2007. Attempts were made to collect updated financial disclosure including that for Jazz Pharmaceuticals. Despite the Sponsor's best efforts, updated financial disclosure information was not obtained for all principal and sub-investigators participating over the 6 year course of the study.

The Applicant states that it acted with due diligence and has no knowledge or reason to believe that any investigators in the 2004-000592033 study or expanded access(2006-05) study received payment in amount over\$ 25,000. Although the Applicant was not able to verify, they are not aware of any investigator that hold significant equity interests in Gentium, or Jazz Pharmaceuticals, Inc.

Financial disclosure information was not provided for the phase 2 dose finding study, (b) (6). The Sponsor provided the following information regarding Study (b) (6). Financial disclosure statements were not collected the Investigator- (b) (6) for investigators participating in this study was not considered a covered study under 21 CFR 54.29(e) at the time the trial was performed. The study was conducted in accordance with the policies of (b) (6) which require mandatory adherence to strict de-minimis limits on the allowable financial interests of investigators participating in clinical research. There were no relevant disclosures, intellectual property or other resources paid to (b) (6) beyond research funding and honoraria with the de-minimus for his activities as part of an advisory committee. In addition, 99-118 study was supported by two Orphan Drug Product grants which in themselves required strict financial disclosure.

A complete list of all investigators participating in study (b) (6) is provided to include for whom the Sponsor has disclosure statements on file as well as a list of investigators for whom there are no disclosure statements.

Clinical Review  
 Tanya Wroblewski, M.D.  
 Donna Przepiorka, M.D. Ph.D.  
 NDA 208114  
 Defitelio (Defibrotide Sodium)

**Covered Clinical Study (Name and/or Number): Study 2006-05**

Was a list of clinical investigators provided:	Yes X <input type="checkbox"/>	No <input type="checkbox"/> (Request list from Applicant)
Total number of investigators identified: <u>243</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>None</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
<p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____</p> <p>Significant payments of other sorts: _____</p> <p>Proprietary interest in the product tested held by investigator: _____</p> <p>Significant equity interest held by investigator in S Sponsor of covered study: _____</p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from Applicant)

**Covered Clinical Study (Name and/or Number): Study R09-1425**

Was a list of clinical investigators provided:	Yes X <input type="checkbox"/>	No <input type="checkbox"/> (Request list from Applicant)
Total number of investigators identified: 13		

Clinical Review  
 Tanya Wroblewski, M.D.  
 Donna Przepiorka, M.D. Ph.D.  
 NDA 208114  
 Defitelio (Defibrotide Sodium)

Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>None</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):  Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from Applicant)

**Covered Clinical Study (Name and/or Number): Study 2004-000592-33**

Was a list of clinical investigators provided:	Yes X <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from Applicant)
Total number of investigators identified: 10		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>None</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		

Clinical Review  
 Tanya Wroblewski, M.D.  
 Donna Przepiorka, M.D. Ph.D.  
 NDA 208114  
 Defitelio (Defibrotide Sodium)

If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S _____ Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from Applicant)

**Covered Clinical Study (Name and/or Number): Study 2005-01**

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from Applicant)
Total number of investigators identified: Refer to Module 1.3.4 for full list of investigators		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>None</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____		

Clinical Review  
 Tanya Wroblewski, M.D.  
 Donna Przepiorka, M.D. Ph.D.  
 NDA 208114  
 Defitelio (Defibrotide Sodium)

Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S _____ Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from Applicant)

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

TANYA M WROBLEWSKI  
02/11/2016

DONNA PRZEPIORKA  
02/11/2016