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# Defibrotide for Patients with Hepatic Veno-Occlusive Disease/Sinusoidal Obstruction Syndrome: Interim Results from a Treatment IND Study

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A B S T R A C T

Hepatic veno-occlusive disease, or sinusoidal obstruction syndrome (VOD/SOS), is a serious and potentially fatal complication of conditioning for hematopoietic stem cell transplantation (HSCT) or of chemotherapy regimens alone. Defibrotide is a complex mixture of single-stranded polydeoxyribonucleotides that is approved in the United States for treating hepatic VOD/SOS with renal or pulmonary dysfunction post-HSCT and in the European Union, Israel, and South Korea for treating severe hepatic VOD/SOS post-HSCT. Defibrotide was previously available in the United States as an investigational drug through a treatment protocol (treatment IND) study. Interim results of that large, treatment IND study of patients with VOD/SOS and with or without multiorgan dysfunction (MOD; also known as multiorgan failure) are presented here. Defibrotide was administered i.v. at 6.25 mg/kg every 6 hours (25 mg/kg/day), with a recommended treatment duration of at least 21 days. Enrolled patients (n = 681) were diagnosed with VOD/SOS based on Baltimore or modified Seattle criteria or liver biopsy analysis. Among the 573 HSCT recipients, 288 (50.3%; 95% confidence interval [CI], 46.2% to 54.4%) were alive at day +100 post-HSCT. Day +100 survival for the pediatric (≤16 years) and adult (>16 years) subgroups was 54.5% (95% CI, 49.1% to 60.0%; n = 174 of 319) and 44.9% (95% CI, 38.8% to 51.0%; n = 114 of 254), respectively. In the MOD subgroup, 159 of 351 patients (45.3%; 95% CI, 40.1% to 50.5%) of patients were alive at day +100 post-HSCT. Treatment with defibrotide was generally well tolerated, and drug-related toxicities were consistent with previous studies. Adverse events were reported in 69.6% of safety-evaluable patients (399 of 573). Other than VOD/SOS and associated MOD symptoms, the most commonly reported treatment-emergent adverse event was hypotension (13.8%). Day +100 survival results observed in this trial were consistent with results seen in previous trials of defibrotide for VOD/SOS in adult and pediatric patients. These data support the potential benefit of defibrotide in treating a VOD/SOS patient population that includes those with and without MOD.



## INTRODUCTION

Hepatic veno-occlusive disease (VOD), also known as sinusoidal obstruction syndrome (SOS), is a potentially life-threatening complication of all conditioning regimens (including reduced-intensity conditioning regimens) for hematopoietic stem cell transplantation (HSCT) or of chemotherapy alone [1-3]. VOD/SOS typically develops during

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the first 21 days following transplantation [2], although delayed onset may occur [4]. The condition is characterized by painful hepatomegaly, hyperbilirubinemia, rapid weight gain, and ascites or fluid retention [1,5].

The reported mean incidence of VOD/SOS is 13.7% (range, 0% to 62.3%) [3]. Even among patients receiving a reduced-intensity conditioning regimen for allogeneic transplantation, the reported incidence of VOD/SOS is approximately 9% [6]. The development of VOD/SOS is influenced by a number of identified risk factors, including pretransplantation patient characteristics (eg, age, previous liver disease, previous treatment with certain chemotherapeutics, genetic factors) and transplantation-related risk factors (eg, graft type, conditioning regimen, graft-versus-host disease [GVHD] prophylaxis regimen) [4,7]. It is believed that damage to endothelial cells induced by cytotoxic chemotherapeutic drugs and radiation, resulting in a prothrombotic-fibrinolytic state, are critical factors in VOD/SOS pathophysiology. Severe VOD/SOS is typically defined by the presence of multiorgan dysfunction (MOD) involving renal and/or pulmonary dysfunction, and is associated with a mortality rate of 80% or higher [3].

Defibrotide is a polydisperse mixture of predominantly single-stranded polydeoxyribonucleotide sodium salts derived from porcine intestinal tissue. Although the mechanism of action of defibrotide is not fully elucidated, preclinical data suggest that it stabilizes endothelial cells by reducing endothelial cell activation, increasing the expression of tissue plasminogen activator and thrombomodulin, while decreasing von Willebrand factor and plasminogen activator inhibitor 1 expression, and by protecting endothelial cells from further damage, resulting in the restoration of thrombofibrinolytic balance [8-15].

In multiple clinical trials, defibrotide has demonstrated efficacy in treating VOD/SOS with MOD following HSCT, as well as for prophylaxis of VOD/SOS in high-risk pediatric HSCT recipients. In a phase III study in pediatric and adult patients with VOD/SOS with MOD following HSCT, treatment with defibrotide was associated with improved day +100 survival post-HSCT (38.2% versus 25.0% for the historical control group; propensity-adjusted, Koch-estimated difference, 23.0%; 95.1% confidence interval [CI], 5.2% to 40.8%; $P = .0109$) and increased complete response rate (25.5% versus 12.5% in the controls; propensity-adjusted, Koch-estimated difference, 19.0%; 95.1% CI, 3.5% to 34.6%; $P = .0160$) [16]. A phase III randomized trial in high-risk pediatric HSCT patients found that prophylaxis with defibrotide resulted in a lower incidence of VOD/SOS by day +30 post-HSCT compared with control patients receiving best supportive care (12% versus 20%; $P = .0507$, log-rank test; $P = .0488$, $Z$ test for competing risk analysis) [17].

In the European Union, defibrotide is indicated for the treatment of severe hepatic VOD/SOS in HSCT therapy for adults and adolescents, children, and infants age >1 month [18]. In the United States, defibrotide was recently approved by the Food and Drug Administration for treatment of adult and pediatric patients with hepatic VOD/SOS with renal or pulmonary dysfunction following HSCT [19]. Before its approval, defibrotide was available in the United States only as an investigational drug as part of clinical trials, and starting in 2007, primarily through an expanded-access treatment protocol (treatment IND) study (ClinicalTrials.gov identifier NCT00628498). This treatment IND study encompasses a broad patient population and is the largest prospective evaluation of defibrotide for treatment of VOD/SOS. Safety and efficacy data (day +100 survival) are presented based on an interim analysis of patients enrolled in the study through December 31, 2013, with available data through December 5, 2014. The overall clinical objectives of this study were to make defibrotide available for patients with VOD/SOS after HSCT or chemotherapy, and to generate prospective data on outcomes in this context.

## METHODS

This multicenter, single-arm, open-label, expanded-access study was designed to assess the safety, tolerability, and survival benefit of defibrotide at day +100 following HSCT in patients with hepatic VOD/SOS with or without MOD.

### *Eligibility Criteria*

Initially, patients were required to have a clinical diagnosis of VOD/SOS according to the Baltimore criteria [20], with bilirubin ≥2 mg/dL and at least 2 of the following: ascites (on radiographic or physical examination), weight gain ≥5% above baseline, and hepatomegaly increased over baseline, by day +35 following HSCT or biopsy-proven VOD/SOS. Patients also were required to have evidence of renal or pulmonary dysfunction by day +45 post-HSCT. Renal dysfunction was defined as serum creatinine ≥3 times the baseline value, creatinine clearance or glomerular filtration rate ≤40% of baseline, or dialysis dependence due to VOD/SOS. Pulmonary dysfunction requirements included oxygen saturation ≤90% on room air, a requirement for supplemental oxygen, or ventilator dependence not due to infection. Patients were excluded from the study if they required any medication that increased risk of hemorrhage, had clinically significant uncontrolled acute bleeding or hemodynamic instability (defined as a need for ≥2 pressors or inability to maintain mean arterial pressure with a single pressor support), or were pregnant.

The study protocol entry criteria were subsequently amended to allow for inclusion of a broader population of patients. An amendment allowed for inclusion of patients with VOD/SOS without MOD, those with non-HSCT VOD/SOS (ie, postchemotherapy), and those with onset of VOD/SOS after day +35. A subsequent amendment also allowed for the inclusion of patients with VOD/SOS as defined by the modified Seattle criteria [21,22], with at least 2 of the following: bilirubin ≥2 mg/dL, ascites and/or weight gain ≥5% above baseline, and hepatomegaly increased over baseline.

The study protocol was approved by each institution's independent institutional review or privacy board, and the study was conducted in accordance with the principles of the Declaration of Helsinki and with local laws and regulations. All patients provided written informed consent and written Health Insurance Portability and Accountability Act authorization where required.

### *Dosing*

Defibrotide was administered as 2-hour i.v. infusions of 6.25 mg/kg every 6 hours (ie, 25 mg/kg/day), with a recommended treatment duration of ≥21 days. Investigators were instructed to continue treatment beyond 21 days until complete response (ie, resolution of symptoms of VOD/SOS and MOD, if present) or discharge from the hospital. Defibrotide administration should have been held for toxicity (grade 3 or 4 significant acute bleeding) or delayed due to medical or surgical procedures. If the toxicity resolved to grade 2 or less, then treatment could be reinitiated; however, treatment was permanently stopped if a drug-related grade 3 or 4 adverse event (AE) recurred, however.

Patients receiving defibrotide were to be assessed daily for bilirubin, fibrinogen, blood urea nitrogen, serum creatinine, complete blood cell and platelet count, prothrombin time, and partial thromboplastin time. Recommended values were platelets, >30,000/mL; hematocrit, >30%; international normalized ratio, <1.5; and fibrinogen, >150 mg/dL.

### *Study Endpoints*

Consistent with the protocol, the primary outcome measure for this interim analysis was survival rate among all patients at day +100 following HSCT. Baseline patient demographic data and disease characteristics were analyzed for the evaluable population of patients who received at least 1 dose of defibrotide, as determined by the following variables: start date, total days, or total doses. The evaluable population was divided into subgroups based on the presence/absence of MOD. The safety population consisted of all patients who received at least 1 dose of defibrotide. Safety assessments included treatment-emergent AEs (TEAEs), treatment-related TEAEs, and serious AEs (SAEs). Medical conditions or diseases present before the start