



Final results from a defibrotide treatment-IND study for patients with hepatic veno-occlusive disease/sinusoidal obstruction syndrome

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Hepatic veno-occlusive disease (VOD), also known as sinusoidal obstruction syndrome (SOS), is a potentially life-threatening complication of conditioning regimens for haematopoietic stem cell transplantation (HSCT) and chemotherapy without HSCT (Bearman *et al*, 1992; Coppel *et al*, 2010; Dignan *et al*, 2013; Kantarjian *et al*, 2017). Diagnosis of VOD/SOS traditionally used the Baltimore (Jones *et al*, 1987) or modified Seattle criteria (McDonald *et al*, 1993) for both adults and paediatric patients. Both sets of criteria assess onset within the initial 20 or 21 days of HSCT (Jones *et al*, 1987; McDonald *et al*, 1993; Carreras *et al*, 2007; Mohty *et al*, 2015). However, onset after 21 days may occur in up to 20% of VOD/SOS patients (Lee *et al*, 1999; Carreras *et al*, 2007; Mohty *et al*, 2015; Richardson *et al*,

Summary

Hepatic veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS) is a potentially life-threatening complication of haematopoietic stem cell transplant (HSCT) conditioning and chemotherapy. Defibrotide is approved for treatment of hepatic VOD/SOS with pulmonary or renal dysfunction [i.e., multi-organ dysfunction (MOD)] after HSCT in the United States and severe VOD/SOS after HSCT in patients aged older than 1 month in the European Union. Defibrotide was available as an investigational drug by an expanded-access treatment programme (T-IND; NCT00628498). In the completed T-IND, the Kaplan–Meier estimated Day +100 survival for 1000 patients with documented defibrotide treatment after HSCT was 58.9% [95% confidence interval (CI), 55.7–61.9%]. Day +100 survival was also analysed by age and MOD status, and *post hoc* analyses were performed to determine Day +100 survival by transplant type, timing of VOD/SOS onset (≤ 21 or > 21 days) and timing of defibrotide treatment initiation after VOD/SOS diagnosis. Day +100 survival in paediatric patients was 67.9% (95% CI, 63.8–71.6%) and 47.1% (95% CI, 42.3–51.8%) in adults. All patient subgroups without MOD had higher Day +100 survival than those with MOD; earlier defibrotide initiation was also associated with higher Day +100 survival. The safety profile of defibrotide in the completed T-IND study was similar to previous reports.

Keywords: defibrotide, haematopoietic stem cell transplant, multi-organ dysfunction, veno-occlusive disease, sinusoidal obstruction syndrome.

2017a; Corbacioglu *et al*, 2018), and the new European Society for Blood and Marrow Transplantation (EBMT) criteria for adults and children now also encompass these later-onset cases (Mohty *et al*, 2016; Corbacioglu *et al*, 2018). Typical characteristics of VOD/SOS in adults include weight gain, painful hepatomegaly, ascites and hyperbilirubinaemia ($\geq 34.2 \mu\text{mol/l}$) (Mohty *et al*, 2016). Characteristics in paediatric patients may also include refractory thrombocytopenia and the recognition that hyperbilirubinaemia may not be present (Corbacioglu *et al*, 2018). The overall mean incidence of VOD/SOS was reported to be 14% in a pooled analysis of 135 studies (Coppel *et al*, 2010). In the setting of reduced-intensity conditioning, one study reported an 8.8% incidence of VOD/SOS (Tsirigotis *et al*, 2014).

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VOD/SOS may progress along a pathophysiological cascade that involves injury to hepatocytes, stellate cells and the sinusoidal endothelium, often in zone 3 of the hepatic acinus, leading to extravasation of blood into the space of Disse and extra-luminal compression of the sinusoids. The pro-thrombotic state resulting from endothelial injury further promotes platelet activation, leading to fibrin deposition, augmented fibrogenesis and hepatic ischaemia. Portal hypertension is a key lesion in VOD/SOS, leading to ascites, volume overload with increased sodium avidity, and injury to pulmonary or renal tissues. Presence of multi-organ dysfunction (MOD), also referred to as multi-organ failure (Carreras, 2012), in patients with VOD/SOS after HSCT is associated with greater than 80% mortality at Day +100 in untreated patients receiving only supportive care (Coppell *et al*, 2010).

Defibrotide is a complex mixture of oligodeoxyribonucleotides derived from porcine mucosal intestinal DNA, and its mechanism of action has been investigated in preclinical studies. Preclinical treatment with defibrotide has been shown to reduce endothelial cell activation; increase expression of thrombomodulin and tissue plasmin activator; decrease expression of von Willebrand factor and plasminogen activator inhibitor-1; reduce activation of nuclear factor- κ B and platelets; protect endothelial cells from further damage (Bianchi *et al*, 1993; Palmer & Goa, 1993; Pescador *et al*, 2013; Richardson *et al*, 2013; Palomo *et al*, 2016); support endothelial-cell function and angiogenesis (Benimetskaya *et al*, 2008); and enhance fibrinolytic activity via plasmin activity (Echart *et al*, 2009). Defibrotide is approved in the European Union (EU) for the treatment of patients >1 month of age who received HSCT and developed severe hepatic VOD/SOS (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002393/WC500153150.pdf). In its recent position statement on VOD/SOS, which includes discussion of treatment options, the EBMT notes that defibrotide is the “only proven” treatment of VOD/SOS (Mohty *et al*, 2015). It is approved in the United States (US) for the treatment of paediatric and adult patients who received HSCT and developed hepatic VOD/SOS with concomitant renal or pulmonary dysfunction (https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/208114Orig1s000Lbl.pdf). Before approval by the US Food and Drug Administration in 2016, defibrotide was available in the US through an expanded-access treatment protocol of an investigational new drug (T-IND; NCT00628498) (Richardson *et al*, 2017a). Presented here are the efficacy and safety results of the completed T-IND study, which is the largest prospective study of defibrotide in patients with VOD/SOS.

Methods

This open-label, single-arm T-IND study was designed to provide expanded access to defibrotide and assess safety and

survival in patients with hepatic VOD/SOS, with or without MOD, post-HSCT or post-non-transplant associated chemotherapy alone, treated with defibrotide. The primary efficacy measure was survival at Day +100 after HSCT or initiation of primary chemotherapy. Safety endpoints included treatment-emergent adverse events (TEAEs) and treatment-related adverse events (TRAEs).

Patient eligibility criteria

Inclusion criteria for the T-IND were originally modelled on the defibrotide phase 3 trial (Richardson *et al*, 2016), which was recruiting at the time, to provide access to defibrotide for those patients not at centres participating in the phase 3 study or who had later onset VOD/SOS with MOD, and therefore were not eligible for the phase 3 study. Inclusion in the T-IND required VOD/SOS, diagnosed by the Baltimore criteria (Jones *et al*, 1987) by Day +35 post-HSCT or by a biopsy, as well as MOD (renal or pulmonary dysfunction) by Day +45 post-HSCT (Richardson *et al*, 2017a). Renal dysfunction was defined as serum creatinine $\geq 3 \times$ baseline value, creatinine clearance or glomerular filtration rate declined to $\leq 40\%$ of baseline, or dialysis dependence due to VOD/SOS. Pulmonary dysfunction was defined as oxygen saturation $\leq 90\%$ on room air, requirement for supplemental oxygen to maintain oxygen saturation $>90\%$, or ventilator dependence not due to infection. When accrual for the phase 3 study ended, the entry criteria for the T-IND were expanded to encompass a broader population of patients, including those with VOD/SOS diagnosed by modified Seattle criteria (McDonald *et al*, 1993), onset of VOD/SOS after Day +35, VOD/SOS after non-transplant associated chemotherapy, and VOD/SOS patients without MOD.

Exclusion criteria included receipt of medications with high risk of haemorrhagic complications, patients with uncontrolled acute bleeding or haemodynamic instability (need for ≥ 2 vasopressors or inability to maintain mean arterial pressure with a single vasopressor), or pregnancy.

Treatment

Defibrotide treatment (25 mg/kg/day: 4 divided doses of 6.25 mg/kg, 2-h infusion) was recommended to be given for ≥ 21 days. Dosing was based on patient's baseline body weight prior to HSCT conditioning: doses were rounded to the nearest 10 mg for adults and paediatric patients >35 kg and to the nearest 5 mg for paediatric patients <35 kg (https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/208114Orig1s000Lbl.pdf). The following blood parameters were monitored and maintained during treatment: haemoglobin >80 g/l, platelet count $>30 \times 10^9$ /l, international normalised ratio (INR) <1.5 with fresh frozen plasma, and fibrinogen >1.5 g/l, with factor replacement as necessary. Per protocol, treatment was recommended to be discontinued or withheld in the following situations: clinically significant

bleeding defined as >15 ml/kg packed red blood cells/24 h or bleeding from a potentially life-threatening site (pulmonary haemorrhage or central nervous system bleeding) irrespective of amount of blood loss. The cause of bleeding was to be treated, and consideration given to resuming treatment at the same dose and infusion volume after bleeding had stopped and the patient was haemodynamically stable. If severe significant bleeding recurred, defibrotide was to be permanently discontinued.

Biostatistics

The planned analyses included Day +100 survival by Kaplan–Meier estimate for all post-HSCT patients receiving ≥ 1 documented dose of defibrotide as well as stratified by age (≤ 16 / >16 years) and MOD status. *Post hoc* analyses of post-HSCT subgroups for Day +100 survival included transplant type (allogeneic transplant *versus* autologous transplant) and time to VOD/SOS onset (≤ 21 days *vs.* >21 days [late onset]). TEAEs were summarised.

An exploratory *post hoc* analysis was conducted to assess the effect of timing of defibrotide initiation post-diagnosis of VOD/SOS on Kaplan–Meier estimate of Day +100 survival using two methods. The first method compared patients starting defibrotide before *versus* after each of the following days: 1, 2, 3, 4, 7 and 14 post-diagnosis by Fisher's exact test for each cut-off day. For the second method, subsets of patients starting defibrotide on a particular day or period only (0, 1, 2, 3, 4, 5, 6, 7, 8–14 and ≥ 15 post-diagnosis) were analysed by Cochran–Armitage trend test across days. Causes of delay were not assessed.

Results

The T-IND included a total of 1154 patients enrolled at 101 centres across the US from 2007 to 2016 who received at least 1 dose of defibrotide post-HSCT or post-non-transplant associated chemotherapy (safety population). Among the 1149 patients from the safety population with available duration of treatment data, the mean (standard deviation) and median length of defibrotide treatment was 21.5 (13.51) and 21.0 days, respectively. Of those enrolled, 1137 met criteria for VOD/SOS (VOD/SOS efficacy population). The Kaplan–Meier estimated Day +100 survival for the efficacy population was 61.1% [95% confidence interval (CI), 58.2–63.9%] and for the 571 patients with MOD was 51.9% (95% CI, 47.6–55.9%). TRAEs were reported in 21.5% of the total population ($N = 1154$). The most common TRAEs were pulmonary haemorrhage (4.3%), gastrointestinal haemorrhage (3.0%), epistaxis (2.3%) and hypotension (2.1%). Serious TRAEs were reported in 11.5% of patients. TRAEs led to discontinuation or death in 12.0% and 2.7% of patients, respectively. The detailed analysis of the non-transplant associated VOD/SOS subgroup is to be reported separately. All subsequent results reported here are from the analysis of the

patient population diagnosed with VOD following HSCT (post-HSCT population) ($n = 1000$).

Demographics of HSCT patients

Baseline characteristics for the treated HSCT patients ($n = 1000$) are shown in Table I and included 570 paediatric patients (≤ 16 years), of whom 28.2% were infants (aged 0–23 months, 161/570), 52.5% were children (aged 2–11 years, 299/570), and 19.3% were adolescents (aged 12–16 years, 110/570). Most of the HSCT patients who developed VOD/SOS received allogeneic transplants (84.3%; median age, 16 years), and the most common primary diseases in this group were acute myeloid leukaemia (260/843; 30.8%) and acute lymphocytic leukaemia (201/843; 23.8%). About half of patients with allografts (441/843; 52.3%) were paediatric. Most patients receiving autologous transplants were paediatric patients (127/155; 81.9%; median age, 4 years), 81.1% (103/127) of whom had a primary diagnosis of neuroblastoma. Neuroblastoma was the primary disease of 66.5% (103/155) of all autograft recipients regardless of age. Other underlying diseases are listed in Table SI. Late-onset VOD/SOS occurred in both adults (169/430; 39.3% of all adult patients) and children (95/570; 16.7%), and 54.5% of all late-onset VOD patients (144/264) had acute leukaemia (Table SII). Transplant types were similar for the groups with late onset and ≤ 21 -day onset (allogeneic: 86.0% and 83.7%; autologous: 14.0% and 16.0%, respectively). The most common graft-versus-host disease (GVHD) prophylaxis in the late-onset group were regimens containing tacrolimus (61.7%), methotrexate (31.4%), ciclosporin (16.3%), and sirolimus (14.8%). Diagnosis of VOD/SOS after Day +100 occurred in 1.1% of patients, and the median day of late-onset VOD/SOS was 29 (range, 22–335).

Efficacy

Kaplan–Meier estimated Day +100 survival of the 1000 patients who had VOD/SOS after HSCT was 58.9% (95% CI, 55.7–61.9%; Fig 1A). In patients with MOD ($n = 512$), Kaplan–Meier estimated Day +100 survival was lower, at 49.5% (95% CI, 45.0–53.8%), compared with 68.9% (95% CI, 64.5–72.9%) in patients without MOD ($n = 488$). The Kaplan–Meier estimated Day +100 survival in paediatric patients was 67.9% (95% CI, 63.8–71.6%) and 47.1% (95% CI, 42.3–51.8%) in adults (Fig 1B).

For the entire post-HSCT population, a *post hoc* trend analysis examining the relationship between Day +100 survival and time to start of defibrotide treatment after VOD/SOS diagnosis found that earlier initiation of defibrotide was associated with higher Day +100 survival ($P < 0.001$, Cochran–Armitage test for trend; Fig 2). The analysis also shows that earlier treatment resulted in improved survival in paediatric patients ($P < 0.001$) and may suggest a similar relationship in adults ($P = 0.055$). Another analysis by cut-off day (Fisher's exact test) showed that earlier treatment initiation compared

Table 1. Baseline demographics and disease characteristics of the HSCT population.

Characteristic	MOD			No MOD			All HSCT		
	Overall (n = 512)	>16 years (n = 231)	≤16 years (n = 281)	Overall (n = 488)	>16 years (n = 199)	≤16 years (n = 289)	Overall (n = 1000)	>16 years (n = 430)	≤16 years (n = 570)
Sex, n (%)									
Male	278 (54.3)	119 (51.5)	159 (56.6)	290 (59.4)	118 (59.3)	172 (59.5)	568 (56.8)	237 (55.1)	331 (58.1)
Female	234 (45.7)	112 (48.5)	122 (43.4)	198 (40.6)	81 (40.7)	117 (40.5)	432 (43.2)	193 (44.9)	239 (41.9)
Race, n (%)									
White	343 (67.0)	175 (75.8)	168 (59.8)	284 (58.2)	135 (67.8)	149 (51.6)	627 (62.7)	310 (72.1)	317 (55.6)
African American	36 (7.0)	13 (5.6)	23 (8.2)	44 (9.0)	16 (8.0)	28 (9.7)	80 (8.0)	29 (6.7)	51 (8.9)
Asian	20 (3.9)	9 (3.9)	11 (3.9)	34 (7.0)	13 (6.5)	21 (7.3)	54 (5.4)	22 (5.1)	32 (5.6)
Latino	71 (13.9)	23 (10.0)	48 (17.1)	92 (18.9)	27 (13.6)	65 (22.5)	163 (16.3)	50 (11.6)	113 (19.8)
Age at time of HSCT, years, median (range)	14.00 (0.10, 69.00)	41.00 (17.00, 69.00)	4.00 (0.10, 16.00)	12.00 (0.10, 77.00)	43.00 (17.00, 77.00)	3.00 (0.10, 16.00)	14.00 (0.10, 77.00)	42.00 (17.00, 77.00)	4.00 (0.10, 16.00)
Conditioning agents (>10%), n (%)									
Cyclophosphamide	333 (65.0)	154 (66.7)	179 (63.7)	241 (49.4)	93 (46.7)	148 (51.2)	574 (57.4)	247 (57.4)	327 (57.4)
Busulfan	262 (51.2)	100 (43.3)	162 (57.7)	301 (61.7)	101 (50.8)	200 (69.2)	563 (56.3)	201 (46.7)	362 (63.5)
Fludarabine	165 (32.2)	88 (38.1)	77 (27.4)	177 (36.3)	97 (48.7)	80 (27.7)	342 (34.2)	185 (43.0)	157 (27.5)
Anti-thymocyte globulin	154 (30.1)	35 (15.2)	119 (42.3)	152 (31.1)	41 (20.6)	111 (38.4)	306 (30.6)	76 (17.7)	230 (40.4)
Total body irradiation	172 (33.6)	104 (45.0)	68 (24.2)	115 (23.6)	66 (33.2)	49 (17.0)	287 (28.7)	170 (39.5)	117 (20.5)
Melphalan	117 (22.9)	30 (13.0)	87 (31.0)	142 (29.1)	38 (19.1)	104 (36.0)	259 (25.9)	68 (15.8)	191 (33.5)
Thiotepa	64 (12.5)	26 (11.3)	38 (13.5)	70 (14.3)	20 (10.1)	50 (17.3)	134 (13.4)	46 (10.7)	88 (15.4)
GVHD prophylaxis, n (%)									
Tacrolimus	250 (48.8)	162 (70.1)	88 (31.3)	233 (47.7)	137 (68.8)	96 (33.2)	483 (48.3)	299 (69.5)	184 (32.3)
Methotrexate	168 (32.8)	101 (43.7)	67 (23.8)	164 (33.6)	82 (41.2)	82 (28.4)	332 (33.2)	183 (42.6)	149 (26.1)
Ciclosporin	159 (31.1)	38 (16.5)	121 (43.1)	123 (25.2)	26 (13.1)	97 (33.6)	282 (28.2)	64 (14.9)	218 (38.2)
Sirolimus	59 (11.5)	47 (20.3)	12 (4.3)	30 (6.1)	26 (13.1)	4 (1.4)	89 (8.9)	73 (17.0)	16 (2.8)
None	73 (14.3)	14 (6.1)	59 (21.0)	108 (22.1)	24 (12.1)	84 (29.1)	181 (18.1)	38 (8.8)	143 (25.1)
Other*	182 (35.5)	74 (32.0)	108 (38.4)	160 (32.8)	66 (33.2)	94 (32.5)	342 (34.2)	140 (32.6)	202 (35.4)
Transplant type,† n (%)									
Allogeneic	450 (87.9)	220 (95.2)	230 (81.9)	393 (80.5)	182 (91.5)	211 (73.0)	843 (84.3)	402 (93.5)	441 (77.4)
Autologous	61 (11.9)	11 (4.8)	50 (17.8)	94 (19.3)	17 (8.5)	77 (26.6)	155 (15.5)	28 (6.5)	127 (22.3)
Primary disease (>10%), n (%)									
AML	142 (27.7)	88 (38.1)	54 (19.2)	119 (24.4)	61 (30.7)	58 (20.1)	261 (26.1)	149 (34.7)	112 (19.6)
ALL	111 (21.7)	48 (20.8)	63 (22.4)	90 (18.4)	49 (24.6)	41 (14.2)	201 (20.1)	97 (22.6)	104 (18.2)
Neuroblastoma	43 (8.4)	1 (0.4)	42 (14.9)	62 (12.7)	0 (0)	62 (21.5)	105 (10.5)	1 (0.2)	104 (18.2)
Prior HSCTs, n (%)									
0	428 (83.6)	189 (81.8)	239 (85.1)	401 (82.2)	162 (81.4)	239 (82.7)	829 (82.9)	351 (81.6)	478 (83.9)
≥1	82 (16.0)	41 (17.7)	41 (14.6)	83 (17.0)	35 (17.6)	48 (16.6)	165 (16.5)	76 (17.7)	89 (15.6)
Unknown/missing	2 (0.4)	1 (0.4)	1 (0.4)	4 (0.8)	2 (1.0)	2 (0.7)	6 (0.6)	3 (0.7)	3 (0.5)
VOD/SOS onset after Day 21, n (%)	139 (27.1)	88 (38.1)	51 (18.1)	125 (25.6)	81 (40.7)	44 (15.2)	264 (26.4)	169 (39.3)	95 (16.7)

Table 1. (Continued)

Characteristic	MOD			No MOD			All HSCT		
	Overall	>16 years	≤16 years	Overall	>16 years	≤16 years	Overall	>16 years	≤16 years
	(n = 512)	(n = 231)	(n = 281)	(n = 488)	(n = 199)	(n = 289)	(n = 1000)	(n = 430)	(n = 570)
Time from diagnosis to start of defibrotide, n (%)									
Day of diagnosis	156 (30.4)	68 (29.4)	88 (31.3)	154 (31.6)	52 (26.1)	102 (35.3)	310 (31.0)	120 (27.9)	190 (33.3)
Day 1	135 (26.4)	63 (27.3)	72 (25.6)	151 (30.9)	49 (24.6)	102 (35.3)	286 (28.6)	112 (26.0)	174 (30.5)
Day 2	68 (13.3)	27 (11.7)	41 (14.6)	57 (11.7)	26 (13.1)	31 (10.7)	125 (12.5)	53 (12.3)	72 (12.6)
Day 3	39 (7.6)	16 (6.9)	23 (8.2)	38 (7.8)	20 (10.1)	18 (6.2)	77 (7.7)	36 (8.4)	41 (7.2)
Day 4	33 (6.4)	15 (6.5)	18 (6.4)	28 (5.7)	12 (6.0)	16 (5.5)	61 (6.1)	27 (6.3)	34 (6.0)
Day 5	17 (3.3)	10 (4.3)	7 (2.5)	19 (3.9)	12 (6.0)	7 (2.4)	36 (3.6)	22 (5.1)	14 (2.5)
Day 6	9 (1.8)	6 (2.6)	3 (1.1)	6 (1.2)	3 (1.5)	3 (1.0)	15 (1.5)	9 (2.1)	6 (1.1)
Day 7	12 (2.3)	5 (2.2)	7 (2.5)	7 (1.4)	4 (2.0)	3 (1.0)	19 (1.9)	9 (2.1)	10 (1.8)
Days 8–14	29 (5.7)	15 (6.5)	14 (5.0)	16 (3.3)	11 (5.5)	5 (1.7)	45 (4.5)	29 (6.7)	19 (3.3)
Day ≥15	14 (2.7)	6 (2.6)	8 (2.8)	12 (2.5)	10 (5.0)	2 (0.7)	26 (2.6)	16 (3.7)	10 (1.8)

ALL, acute lymphocytic leukaemia; AML, acute myelogenous leukaemia; GVHD, graft-versus-host disease; HSCT, haematopoietic stem cell transplant; MOD, multi-organ dysfunction; VOD/SOS, veno-occlusive disease/sinusoidal obstruction syndrome.

*Includes medications that were not prespecified on the case report form.

†Transplant type unknown for two patients.

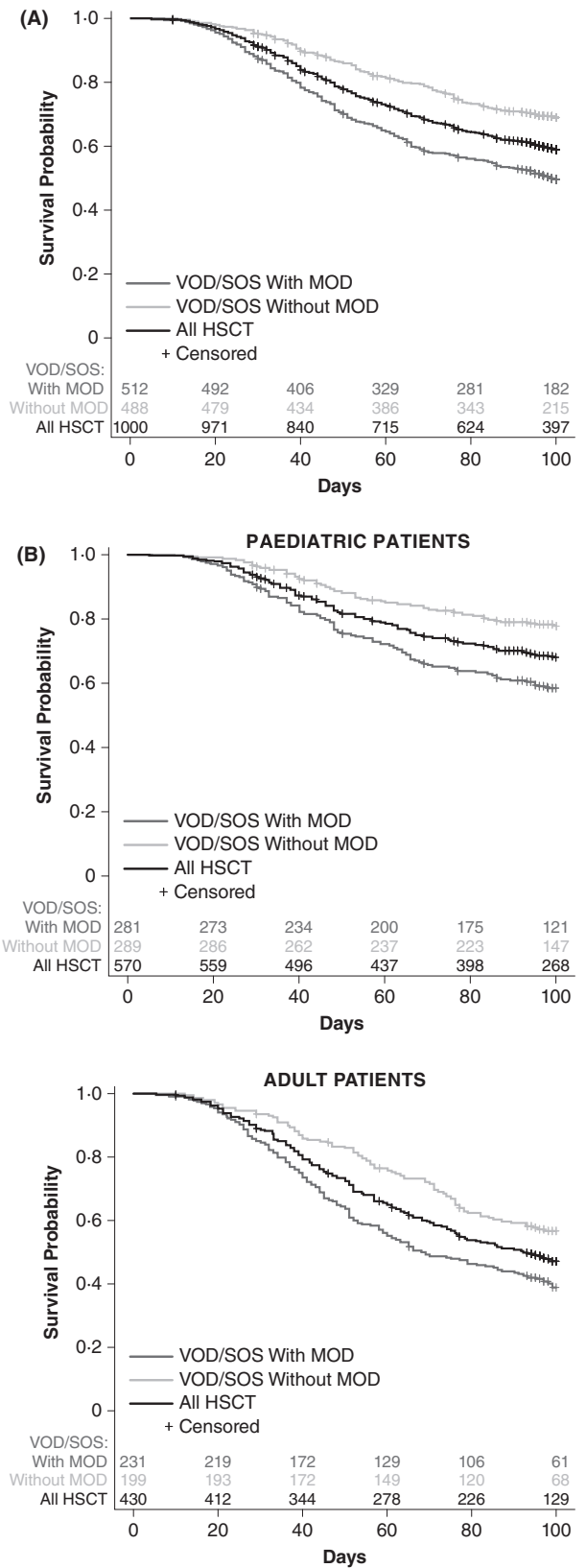


Fig 1. Kaplan–Meier estimated survival to Day +100 by MOD status (panel A) and age and MOD-status subgroup (panel B), HSCT population. HSCT, haematopoietic stem cell transplant; MOD, multi-organ dysfunction; VOD/SOS, veno-occlusive disease/sinusoidal obstruction syndrome.

with later initiation after VOD/SOS diagnosis was associated with significantly higher Day +100 survival ($P \leq 0.001$) at all time points except Day 14 post-diagnosis (2.6% of patients started after Day 14 post-diagnosis). Individual cut-off days were significant ($P \leq 0.003$) for all days except Day 14 post-diagnosis in the MOD subgroup, and in the subgroup without MOD ($P < 0.041$) except for Day 2 post-diagnosis. Reasons for treatment delay were not assessed.

Regardless of graft source, patients without MOD had higher survival than patients with MOD. Paediatric patients with autologous grafts and VOD/SOS, regardless of MOD status, had higher survival than those with allogeneic grafts. The pattern was generally similar for adult patients; however, only 7.0% received autologous grafts (Fig 3).

Paediatric patients with late-onset VOD/SOS had a Kaplan–Meier estimated Day +100 survival of 60.4% (95% CI, 49.5–69.7%), and adults, 48.7% (95% CI, 40.9–56.0%) (Fig 4). In patients with late-onset VOD/SOS and MOD, Kaplan–Meier estimated survival in the paediatric subgroup was 45.4% (95% CI, 31.0–58.6%) and 43.0% (95% CI, 32.5–53.0%) in adults, while estimated survival in patients with MOD was 78.4% (95% CI, 62.5–88.1%) in paediatric patients and 55.1% (95% CI, 43.5–65.2%) in adults. Paediatric patients who were diagnosed with late-onset VOD/SOS with MOD had numerically lower Day +100 survival (45.4%; 95% CI, 31.0–58.6%) than paediatric patients diagnosed in ≤ 21 days (60.9%; 95% CI, 54.2–66.9%); however, similar Kaplan–Meier estimated Day +100 survival was observed in both onset subgroups of adults (Fig 4).

Treatment with sirolimus has been associated with development of VOD/SOS (Cutler *et al*, 2008), and among patients receiving sirolimus at baseline ($n = 90$; primarily adults), 66.7% (60/90) had MOD, compared with 49.7% (452/910) in patients who did not receive sirolimus (majority paediatric). A *post hoc* analysis showed that Day +100 survival was 53.8% (95% CI, 48.2–63.6%), compared with 59.4% (95% CI, 56.0–62.5%) for patients not receiving sirolimus. Per protocol, concomitant use of sirolimus was not recommended.

Safety profile

Age, MOD status, and transplant type were associated with some apparent variations in safety profiles. Adult patients had higher rates of TEAEs than paediatric patients, while patients with MOD had higher rates than patients without MOD (Table II). Two hundred and ten patients (21%) had ≥ 1 TEAE as assessed by investigators as being at least possibly related to treatment (TRAE). Similar rates of TRAEs were observed in the late-onset (20.8%) and ≤ 21 -days onset (21.1%) subgroups. TRAEs led to discontinuation in 124 patients (12.4%) and death in 28 patients (2.8%). TRAEs that occurred in $\geq 2\%$ of patients were pulmonary haemorrhage (4.6%), gastrointestinal haemorrhage (3.0%), epistaxis (2.3%) and hypotension (2.0%). The incidence of TRAEs

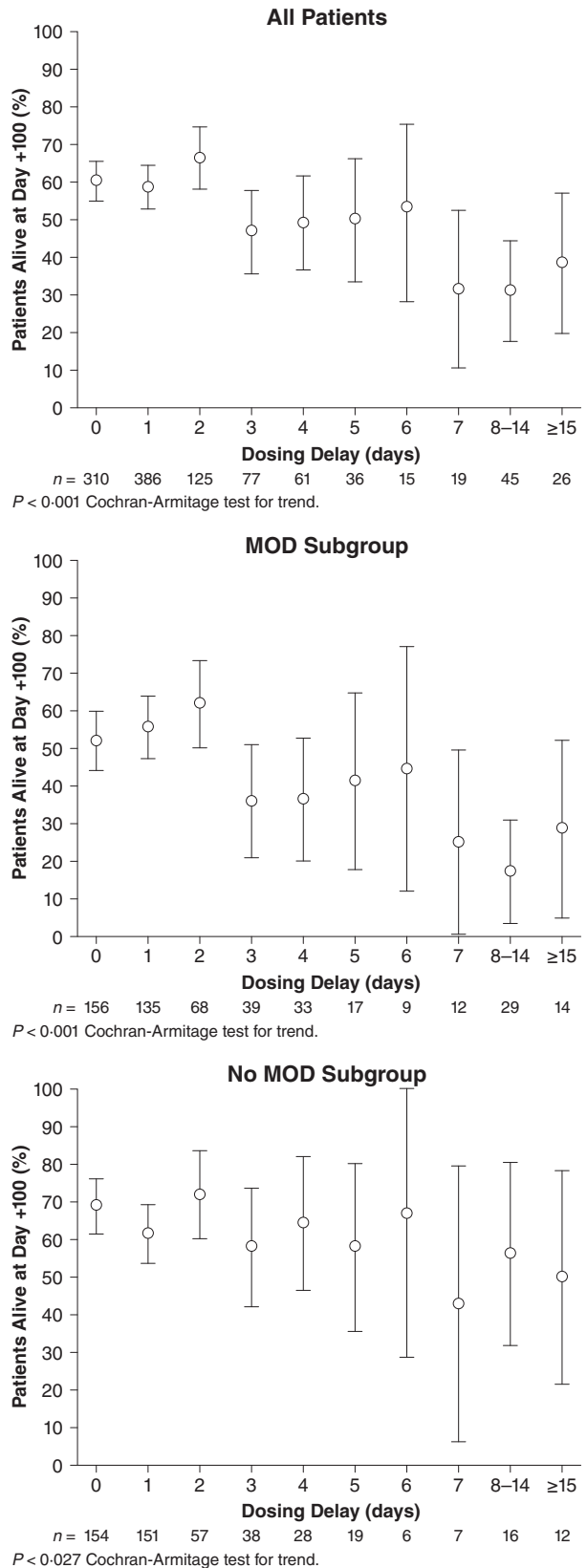


Fig 2. Timing of initiation of defibrotide after VOD/SOS diagnosis. MOD, multi-organ dysfunction; VOD/SOS, veno-occlusive disease/sinusoidal obstruction syndrome.

appeared to be generally similar in paediatric and adult patients, although the incidence of specific TRAEs varied by age. TRAEs that occurred in $\geq 2\%$ of adults were epistaxis (3.5%), gastrointestinal haemorrhage (3.5%), pulmonary haemorrhage (2.3%), haematuria (2.1%) and hypotension (2.1%). TRAEs that occurred in $\geq 2\%$ of paediatric patients were pulmonary haemorrhage (6.3%) and gastrointestinal haemorrhage (2.6%). Epistaxis and gastrointestinal haemorrhage appeared to be more frequent in

adult patients than in paediatric patients (epistaxis: 1.4% in paediatric patients). Pulmonary haemorrhage and lower gastrointestinal haemorrhage appeared to be more frequent in paediatric patients than adult patients (lower gastrointestinal haemorrhage: 1.1% in paediatric patients and 0.5% in adults). By transplant type, TRAEs occurred in 21.2% of patients who received an allogeneic HSCT and 20.0% of those who received an autologous HSCT. The most common TRAEs ($>2\%$) in either graft subgroup were

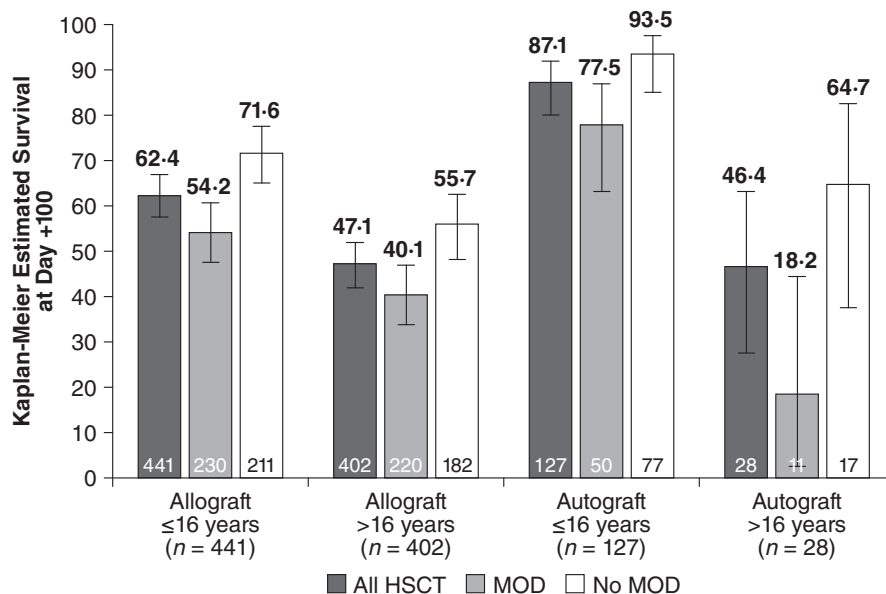


Fig 3. Kaplan–Meier estimated Day +100 survival by transplant type. HSCT, haematopoietic stem cell transplant; MOD, multi-organ dysfunction.

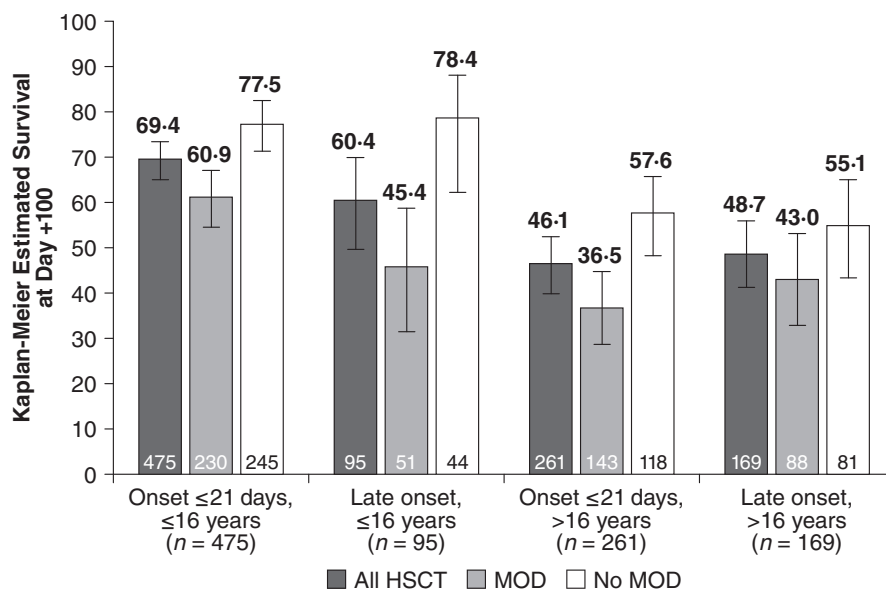


Fig 4. Comparison of Kaplan–Meier estimated Day +100 survival by time of VOD/SOS onset post-HSCT. HSCT, haematopoietic stem cell transplant; MOD, multi-organ dysfunction; VOD/SOS, veno-occlusive disease/sinusoidal obstruction syndrome.

Table II. Safety profile of total HSCT population.

TEAE, n (%)	MOD			No MOD			All HSCT		
	>16 years (n = 231)	≤16 years (n = 281)	Overall (n = 488)	>16 years (n = 199)	≤16 years (n = 289)	Overall (n = 1000)	>16 years (n = 430)	≤16 years (n = 570)	
	Overall (n = 512)	Overall (n = 281)	Overall (n = 488)	Overall (n = 199)	Overall (n = 289)	Overall (n = 1000)	Overall (n = 430)	Overall (n = 570)	
≥1 TEAE	187 (81.0)	198 (70.5)	324 (66.4)	148 (74.4)	176 (60.9)	709 (70.9)	335 (77.9)	374 (65.6)	
≥1 Serious TEAE	151 (65.4)	159 (56.6)	227 (46.5)	105 (52.8)	122 (42.2)	537 (53.7)	256 (59.5)	281 (49.3)	
≥1 Treatment-related TEAE	50 (21.6)	68 (24.2)	92 (18.9)	38 (19.1)	54 (18.7)	210 (21.0)	88 (20.5)	122 (21.4)	
≥1 Haemorrhage	77 (33.3)	89 (31.7)	124 (25.4)	55 (27.6)	69 (23.9)	290 (29.0)	132 (30.7)	158 (27.7)	
≥1 Hypotension	47 (20.3)	31 (11.0)	42 (8.6)	23 (11.6)	19 (6.6)	120 (12.0)	70 (16.3)	50 (8.8)	

HSCT, haematopoietic stem cell transplant; MOD, multi-organ dysfunction; TEAE, treatment-emergent adverse event.

pulmonary haemorrhage (allogeneic 4.9%; autologous 3.2%), gastrointestinal haemorrhage (allogeneic 3.3%; autologous 1.3%), epistaxis (allogeneic 2.4%; autologous 1.9%) and hypotension (allogeneic 1.9%; autologous 2.6%). The safety profile of defibrotide in the completed T-IND study was similar to previous reports.

Discussion

The findings of the completed T-IND in the 1000 patients who received HSCT, all of whom received defibrotide, showed an overall Kaplan–Meier estimated Day +100 survival of 58.9%. Day +100 survival was 67.9% in paediatric patients and 47.1% in adults and, consistent with prior reports (Richardson *et al*, 2010, 2017a; Corbacioglu *et al*, 2016; Strouse *et al*, 2016), was higher in patients without MOD (68.9%) than in patients with MOD (49.5%). *Post hoc* analyses suggest that time of VOD/SOS onset and timing of initiation of defibrotide treatment after diagnosis affected patient outcomes.

The HSCT population of the final report ($n = 1000$) is substantially larger than for the interim analysis ($n = 573$, data up to 5 December 2014) (Richardson *et al*, 2017a), and the findings were consistent. Importantly, the 427 additional patients were enrolled between 31 December 2013, and study closure on 4 April 2016, and thus represent a near-contemporary clinical population. The Kaplan–Meier estimates of Day +100 survival for post-HSCT patients of the interim and completed T-IND analyses were 53.8% (Richardson *et al*, 2017a) and 58.9%, respectively. The higher proportion of patients without MOD in the completed T-IND (49%) than in the interim report (39%) (Richardson *et al*, 2017a), presumably due to change in enrolment criteria, may have contributed to the somewhat higher survival in the completed study. The patient population at the interim and completed time points were similar in age (age ≤16: 56% vs. 57%) and experienced similar rates and types of TRAEs (Richardson *et al*, 2017a).

The T-IND results in patients with and without MOD who were treated with defibrotide are consistent with other reports, including the Compassionate Use Program (CUP) results (Corbacioglu *et al*, 2016). The CUP programme collected data on patients with VOD/SOS with or without MOD who were treated with defibrotide (median dose, 25 mg/kg/day; range, 10–80 mg/kg/day); 89% of patients had received HSCT. The overall Day +100 survival was 54% and was 58% in patients who received defibrotide 25 mg/kg/day, which is a result similar to that in the T-IND HSCT patients. The patients without MOD from the CUP study had a survival at Day +100 of 65% (Corbacioglu *et al*, 2016), comparable to the 68.9% survival of the T-IND subgroup without MOD. Further, the T-IND also included detailed results by age group as well as *post hoc* subgroup analyses by transplant type and time to onset of VOS/SOS, in addition to analysing timing of initiation of defibrotide after VOD/SOS diagnosis.

The similar overall findings in the present report build on those of the CUP, because the T-IND included a formal protocol and one dose level of defibrotide with mandatory reporting of safety and survival, while reporting in the CUP was voluntary and data were provided for 710 of the 1129 patients provided with defibrotide at a range of suggested doses (Corbacioglu *et al*, 2016).

Among patients with MOD, the CUP study reported a Day +100 survival of 39.7% (Corbacioglu *et al*, 2016), which is similar to that reported for the treatment group in the phase 3 historically controlled trial (38.2%) (Richardson *et al*, 2016). In the phase 2 dose-finding study of defibrotide, Day +100 survival was 46% in the 25 mg/kg/day arm and 42% in the 40 mg/kg/day arm (Richardson *et al*, 2010). In addition, a retrospective analysis of the Center for International Blood & Marrow Transplant Research (CIBMTR) database of patients with VOD/SOS and MOD who were treated with defibrotide reported a Day +100 survival of 39% (Strouse *et al*, 2016). Overall, the results from these other studies are generally supportive of the 49.5% Day +100 survival in the MOD subgroup of this T-IND study.

The phase 3 trial and the CIBMTR registry analysis also included Day +100 survival results for patients with MOD who did not receive defibrotide and reported survival of 25% and 30.9%, respectively (Richardson *et al*, 2016; Strouse *et al*, 2016). In addition, a Japanese registry reported survival in a cohort (84% aged ≥ 16 years) treated with plasma, urso-diol, antithrombin III and/or heparin ($>30\%$ each), but only 5% received defibrotide (Yakushijin *et al*, 2016). In that analysis, the Day +100 survival was 15% in patients with VOD/SOS and MOD and 44% in patients without MOD (Yakushijin *et al*, 2016). Similarly, the CIBMTR analysis of VOD/SOS with MOD included patients not receiving defibrotide and found survival of 27.3% in adults and 45.5% in paediatric patients (Strouse *et al*, 2016). Of note, untreated patients in the CIBMTR analysis had somewhat lower rates of organ dysfunction than treated patients (pulmonary: 43.6% vs. 53.7%; renal: 67.3% vs. 70.7%) (Strouse *et al*, 2016).

More than 30% of patients were treated on the day of VOD/SOS diagnosis (more than 70% within the first 2 days), and earlier initiation of defibrotide treatment after diagnosis yielded higher Day +100 survival by cut-off days and for the trend test, which is similar to the T-IND interim results (Richardson *et al*, 2017b). Per protocol, treatment was to begin as soon as the patient met eligibility requirements; the causes of delay in treatment initiation were not assessed. These findings suggest that defibrotide initiation should not be delayed once VOD/SOS has been diagnosed, which is consistent with guidelines from the British Committee for Standards in Haematology/British Society for Blood and Marrow Transplantation and the EBMT, which emphasise prompt initiation of treatment “at a stage when the disease is in a more favourable response state” (Dignan *et al*, 2013; Mohty

et al, 2016). Although these results suggest that it may be beneficial to initiate treatment as early as possible in patients meeting EBMT diagnostic criteria, irrespective of MOD status, rather than waiting for further development of the disease to MOD, the absence of a control limits interpretation of these data.

By transplant type, the survival in recipients of autologous transplants probably reflects the younger age of patients in this group (82% age ≤ 16 years) and diagnosis of a solid tumour (80% neuroblastoma, a disease of very young children) compared with allogeneic transplants (52% age ≤ 16 years), with primary diagnoses of acute leukaemia (54%). A single institution retrospective report showed very high responses to high-dose methylprednisolone in 9 paediatric patients with VOD/SOS (5 allogeneic and 4 autologous transplants), 4 of whom also received defibrotide (Myers *et al*, 2013). Overall survival was 78%, with a Day +100 survival of 89%. In a subsequent retrospective study at the same institution (Gloude *et al*, 2018), 15 additional patients with VOD/SOS (8 allogeneic and 7 autologous transplants) were treated with both high-dose methylprednisolone and defibrotide and had a Day +100 survival of 73%. Of note, 6 of the patients had a primary diagnosis of neuroblastoma. The authors suggest further study of defibrotide with high-dose steroids (Gloude *et al*, 2018).

Late-onset (>21 days after HSCT) VOD/SOS Day +100 estimated survival was 52.8%, which was similar to the overall HSCT population (58.9%). Late-onset and \leq Day-21 onset VOD/SOS Day +100 estimated survival was similar in the paediatric subgroups and in the adult subgroups. In recognition of the occurrence of VOD/SOS >21 days (Jones *et al*, 1987; Mohty *et al*, 2015), EBMT criteria for adults now include a late-onset category (Mohty *et al*, 2016). In addition, onset >21 days occurs in approximately 20% of paediatric cases (Corbacioglu *et al*, 2016, 2018) and thus, the EBMT paediatric criteria do not include time parameters for diagnosis, to acknowledge and include the presence of VOD/SOS onset before and after Day 21 (Corbacioglu *et al*, 2018). The frequency of VOD/SOS after Day 21 found in this study (26.4%) as well as others (Lee *et al*, 1999; Carreras *et al*, 2007; Mohty *et al*, 2015; Corbacioglu *et al*, 2018), reinforces the importance of continued vigilance for occurrence of late-onset VOD/SOS. Importantly, in one study, diagnosis of late-onset VOD/SOS in adult patients ranged from 8 to 43 days after hospital discharge and was more prevalent in patients conditioned with busulfan and melphalan (Bu/MEL; 52%) than other conditioning regimens (Carreras *et al*, 2007). Ten of 11 patients in the Bu/MEL subgroup who developed VOD/SOS after hospital discharge required readmission (Carreras *et al*, 2007). The finding that late-onset VOD/SOS was more frequent in adults than paediatric patients was unexpected because late-onset VOD/SOS is generally thought to be more common in paediatric patients (Corbacioglu *et al*, 2018). However, this study may underestimate the true incidence of late-onset VOD/SOS due to restrictions in the initial protocol

requiring diagnosis by Day +35 or could reflect differences in the disease or treatment response by age group.

The safety profile in this completed T-IND is consistent with prior studies (Richardson *et al*, 2010, 2016, 2017a; Corbacioglu *et al*, 2012a, 2016), including the general overlap of safety profile and types of TRAEs seen between adult patients and paediatric patients (Corbacioglu *et al*, 2016; Richardson *et al*, 2017a). An important consideration when assessing any possible causal association between TEAEs and defibrotide therapy is the high rate of reported TEAEs in this very ill patient population, which is illustrated by control populations in prior defibrotide clinical trials (Corbacioglu *et al*, 2012b; Richardson *et al*, 2016). In the historically controlled treatment study, overall TEAEs occurred in virtually all patients (101/102), with hypotension and haemorrhagic events occurring in 39% and 64% in the defibrotide arm and in 50% and 75% of historical controls (Richardson *et al*, 2016). In the randomised prophylaxis study, haemorrhagic TEAEs occurred in similar proportions of the defibrotide (22%) and control (21%) groups, and overall adverse event rates were 87% and 88% in the prophylaxis and control groups, respectively (Corbacioglu *et al*, 2012b).

Among the key strengths of this T-IND study are its size, as it is the largest prospective analysis of defibrotide treatment of patients with VOD/SOS after HSCT ($n = 1000$); real-world use (reflected by the diversity of its patients by age, conditioning regimen, type of transplant, presence or absence of MOD and treated at 101 centres); and its essentially contemporary population, with >40% enrolled between December 2013 and April 2016. Acknowledged limitations include that this T-IND was designed to provide access to defibrotide and was therefore a single-arm study with limited data monitoring; however, it followed a larger population of defibrotide-treated patients with MOD ($n = 512$) than the treated population in the combined phase 2 and phase 3 studies ($n = 251$) (Richardson *et al*, 2010, 2016). The results of this larger defibrotide-treated population were consistent with previous studies, and the large population allowed a wide range of subgroup analyses for uncommon presentations.

Conclusions

This large prospective expanded-access study found efficacy of defibrotide treatment of VOD/SOS in multiple patient subgroups: paediatric (≤ 16 years) and adult (> 16 years) patients, patients with VOD/SOS with or without MOD, patients receiving allogeneic and autologous transplants, and patients with VOD/SOS onset ≤ 21 days and > 21 days post-HSCT. Moreover, earlier treatment after diagnosis of VOD/SOS was associated with higher Day +100 survival. The safety profile of defibrotide treatment was similar to previous studies, with no new types of TRAEs.

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Author contributions

P.G.R., R.J.S. and R.H. were responsible for the study conception and design. N.A.K., S.A.G., A.R.S., S.A., B.M.T., J.H.A., L.L., T.S., V.T.H., N.B., M.I., W.L., R.H., W.T., R.J.S. and P.G.R. were involved in the collection and assembly of data. All authors participated in the study data analysis and interpretation, contributed to the manuscript writing, and provided their final approval of this manuscript.

Disclosures

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Table SI. Underlying primary diseases for HSCT.

Table SII. Demographics of the patient subgroups by late-onset or non-late-onset VOD/SOS.

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