EMA/CHMP/PRAC/273786/2022
Committee for Medicinal Products for Human Use (CHMP)
Pharmacovigilance Risk Assessment Committee (PRAC)

Assessment report

Defitelio

International non-proprietary name: defibrotide

Procedure No. EMEA/H/C/002393/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Start of procedure	11 May 2021	11 May 2021	☐
☐	CHMP Rapporteur Assessment Report	14 Jun 2021	16 Jun 2021	☐
☐	PRAC Rapporteur Assessment Report	21 Jun 2021	16 Jun 2021	☐
☐	PRAC members comments	25 Jun 2021	25 Jun 2021	☐
☐	CHMP members comments	28 Jun 2021	28 Jun 2021	☐
☐	Updated PRAC Rapporteur Assessment Report	29 Jun 2021	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	01 Jul 2021	n/a	☐
☐	Start of written procedure	06 Jul 2021	06 Jul 2021	☐
☐	PRAC endorsed relevant sections of the assessment report[3]	06 Jul 2021	06 Jul 2021	☐
☐	Request for Supplementary Information (RSI) or Opinion	08 Jul 2021	08 Jul 2021	☐
☐	Submission Deadline	27 Aug 2021	27 Aug 2021	☐
☐	Re-start Date	31 Aug 2021	31 Aug 2021	☐
☐	CHMP Rapporteur Assessment Report	04 Oct 2021	04 Oct 2021	☐
☐	PRAC Rapporteur Assessment Report	11 Oct 2021	04 Oct 2021	☐
☐	PRAC members comments	15 Oct 2021	15 Oct 2021	☐
☐	CHMP members comments	18 Oct 2021	18 Oct 2021	☐
☐	Updated PRAC Rapporteur Assessment Report	19 Oct 2021	19 Oct 2021	☐
☐	Updated CHMP Rapporteur Assessment Report	21 Oct 2021	N/A	☐
☐	PRAC Outcome	26 Oct 2021	26 Oct 2021	☐
☐	2nd Request for Supplementary Information (RSI) or Opinion	28 Oct 2021	28 Oct 2021	☐
☐	Submission Deadline	10 Jan 2022	10 Jan 2022	☐
☐	Re-start Date	11 Jan 2022	11 Jan 2022	☐
☐	CHMP Rapporteur Assessment Report	14 Feb 2022	14 Feb 2022	☐
☐	PRAC Rapporteur Assessment Report	21 Feb 2022	14 Feb 2022	☐
☐	PRAC members comments	25 Feb 2022	25 Feb 2022	☐
☐	CHMP members comments	28 Feb 2022	28 Feb 2022	☐
☐	Updated PRAC Rapporteur Assessment Report	01 Mar 2022	01 Mar 2022	☐

Status of this report and steps taken for the assessment				
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☐	Start of written procedure	n/a	n/a	☐
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☐	Submission Deadline	06 Apr 2022	06 Apr 2022	☐
☐	Re-start Date	07 Apr 2022	07 Apr 2022	☐
☐	CHMP Rapporteur Assessment Report	20 Apr 2022	22 Apr 2022	☐
☐	PRAC Rapporteur Assessment Report	22 Apr 2022	22 Apr 2022	☐
☐	PRAC members comments	25 Apr 2022	25 Apr 2022	☐
☐	CHMP members comments	25 Apr 2022	25 Apr 2022	☐
☐	Updated PRAC Rapporteur Assessment Report	26 Apr 2022	26 Apr 2022	☐
☐	Updated CHMP Rapporteur Assessment Report	28 Apr 2022	28 Apr 2022	☐
☐	PRAC Outcome	05 May 2022	05 May 2022	☒
☒	Opinion	19 May 2022	19 May 2022	☒

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List of abbreviations

ALL	Acute Lymphoblastic Leukaemia
AML	Acute Myelogenous Leukaemia
ANG2	Angiopoietin 2
BSC	Best Supportive Care
CIBMTR	Center for International Blood and Marrow Transplant Research
DP	Defibrotide Prophylaxis
EBMT	European Society for Blood and Marrow Transplantation
EPAC	Endpoint Adjudication Committee
GvHD	Graft-versus-host disease
HSCT	Hematopoietic Stem Cell Transplantation
MOD/MOF	Multi-organ dysfunction/multi-organ failure
NRM	Non-relapse mortality
OP	Osteopetrosis
PAI-1	Plasminogen activator inhibitor-1
SADR	Serious adverse drug reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOB	Specific Obligation
SOC	System Organ Class
(s)-VOD	(severe)-veno-occlusive disease
t-PA	tissue plasminogen activator
UDCA	Ursodeoxycholic acid
vWF	von Willebrand factor

1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Gentium S.r.l. submitted to the European Medicines Agency on 11 May 2021 an application for a variation.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.11.b	C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required	Type II	I, IIIA and IIIB

Submission of the final report from study 15-007 listed as a specific obligation in the Annex II of the Product Information. This is a phase 3, randomised, adaptive study (15-007) of Defibrotide vs. best supportive care in the prevention of hepatic veno-occlusive disease in adult and paediatric patients undergoing hematopoietic stem cell transplant (HSCT). The RMP version 9 has also been submitted.
The MAH has also taken the opportunity to align the PI to the latest QRD template 10.2 which replaces the United Kingdom with United Kingdom (Northern Ireland) in the PIL.
In addition, the MAH is correcting the following errata during the linguistic review of the PI: correction of the paragraph number for Regulation (EC) No 726.2004 which was cited incorrectly in Annex II of the French PI and formatting updates to Norwegian and Swedish language PIs.

The requested variation proposed amendments to the Summary of Product Characteristics, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

2. Overall conclusion and impact on the benefit/risk balance

Defitelio (defibrotide) was granted an MA under exceptional circumstances in 2013 after a re-examination procedure, based on retrospective data and small prospective studies with historical controls, for the treatment of severe hepatic veno-occlusive disease (VOD) also known as sinusoidal obstruction syndrome (SOS) in haematopoietic stem-cell transplantation (HSCT) therapy in adults, adolescents, children and infants over 1 month of age. VOD/SOS belongs to a group of transplant-related, systemic endothelial diseases and is a potentially life-threatening complication of HSCT, triggered by several factors including toxicity of the conditioning regimen. With the MA, one specific obligation (SOB) of a Post-Approval Safety Study (PASS) was agreed, however, this PASS was found not feasible, and a new list of SOBs were agreed within procedure EMEA/H/C/002393/II/0027, see section 5 for full list of SOBs.

The new SOB 1, which is a Category 2 study and the scope for this procedure, reads: "In order to collect comparative safety data, the MAH will provide the final CSR and a report of comparative safety data from the Phase 3, randomised, adaptive study (15-007) of Defibrotide vs best supportive care in the prevention of hepatic veno-occlusive disease in adult and paediatric patients undergoing hematopoietic stem cell transplant (HSCT). The report will also reflect on the safety data being collected during prophylactic treatment, and any potential safety differences related to the difference in indication (i.e., treatment vs prophylactic therapy)." The safety concerns addressed by this study are Haemorrhage, Hypotension, Coagulopathy, Immunogenicity, Thromboembolic events, Patients treated concomitantly with defibrotide and medications that increase the risk of haemorrhage

(including the newer oral anti-coagulants direct thrombin and factor Xa inhibitors), Patients with pre-existing liver or severe renal insufficiency (aetiologies other than VOD) and Patients with intrinsic lung disease.

The MAH proposed initially to update the product information Annex II by removing this study from the list of SOBs and to update the RMP accordingly. No other significant changes to the product information were proposed by the MAH. Within subsequent rounds, however, an update of 5.1 has also been included. Although use of defibrotide for prophylaxis of VOD is not covered by the approved indication, the prophylaxis studies contain paediatric data and are thus to be included in section 5.1.

Study 15-007 was a randomised open-label study aimed at assessing the prophylactic effect of adding defibrotide to standard of care in a population (adults and children >1 month of age) undergoing HSCT with assumed (very) high risk of VOD. Prevention of VOD is not an approved indication for Defitelio. However, subjects included who developed VOD based on investigators judgement would receive defibrotide as rescue treatment, which is according to the label albeit for severe VOD only. The study was stopped after an interim analysis based on futility; 372 subjects were randomised which was in line with the originally anticipated study size.

The primary efficacy endpoint (VOD-free survival rate by Day +30 post-HSCT) was not met; there was no preventive effect of defibrotide on VOD-free survival day 30+ post-HSCT in the defibrotide group as compared to best supportive care. There was a numerical imbalance in favour of best supportive care; this was particularly pronounced in the paediatric population. In the overall ITT population, VOD/death occurred in 50/190 subjects in the defibrotide arm (26.3%) and 40/182 subjects in the BSC arm (22%). The KM VOD-free survival estimates (95% CIs) at Day +30 post-HSCT in the defibrotide arm vs the BSC arm were 66.8% (57.8%, 74.4%) and 72.5% (62.3%, 80.4%), respectively. In the paediatric population, VOD/death occurred in 32/104 subjects in the defibrotide arm (30.8%) and 20/94 subjects in the BSC arm (21.3%). The KM VOD-free survival estimates (95% CIs) at Day +30 post-HSCT in the paediatric defibrotide arm vs the BSC arm were 62.5% (95% CI 50.2%, 72.5%) and 75.0% (95% CI 63.7%, 83.2%), respectively. There were 10 deaths up to day 30-post-HSCT in the defibrotide group and 5 in the best supportive care group. Of these, 6 were paediatric participants (defibrotide group, n=4; best supportive care group, n=2), and 9 were adult participants (defibrotide group n=6; best supportive care group, n=3).

One strength of study 15-007 as compared to previous defibrotide studies was the independent blinded assessment of the primary efficacy endpoint, demonstrating a discrepancy between the blinded, independent assessment of VOD and investigator's assessment of VOD. This discrepancy has been explained by the MAH in that the blinded independent assessment of VOD was inaccurate. Notably, both investigators and the blinded independent assessment of VOD relied on the modified Seattle criteria, which appears reasonable to use also in a retrospective assessment of data given that appropriate data are provided for the assessment; since this appears to have been the case, the MAH view is not found justified. Patients diagnosed as VOD by the EPAC only, and not receiving 'rescue treatment' with defibrotide had a clearly more favourable outcome regarding mortality. The MAH argumentation that those diagnosed by the EPAC actually did not have VOD or had very mild VOD translating into a better prognosis as compared to more severe VOD as diagnosed by investigators, has not been supported by actual clinical data. Thus, no firm conclusions can be drawn, and it is not likely that additional analyses could be of value. Notably, the discordance between investigators and the EPAC may not only be accounted for by the investigator being close to the patient, as argued by the MAH, but also by an underlying bias resulting from investigators being non-blinded to study treatment.

Overall, the safety data from study 15-007 that are considered of most relevance are the data from the prophylaxis period when defibrotide was administered to subjects in the defibrotide arm (up to Day

+30 post-HSCT), and the data from the rescue treatment period (when subjects diagnosed as VOD by investigators received defibrotide). Serious treatment-related TEAEs during both the prophylaxis and treatment periods include bleeding events, which is expected given the known safety profile of defibrotide. For mortality, the numerical imbalance in favour of best supportive care regarding VOD-free mortality was considered to potentially be of relevance also for the approved indication, since the population studied is similar to the population covered by the approved indication. Further, the aim of this study as outlined in the list of SOBs was also to assess any potential safety differences related to the difference in indication (I e, treatment vs prophylactic therapy). An in-depth discussion was requested in previous rounds to address the safety profile and the apparent imbalance in mortality with defibrotide treatment also in relation to the approved indication, with a separate discussion on the paediatric population regarding survival. In that respect, non-relapse mortality (which was a secondary endpoint in study 15-007, pertaining to those with malignant disease at baseline which was the vast majority of study participants) was found worrisome in that 22 of 147 participants (15.0%) in the defibrotide prophylaxis arm and 11 of 139 participants (7.9%) in the BSC arm experienced NRM by Day +100 post-HSCT. All subjects in the rescue phase received defibrotide, therefore, the impact of the initial randomised groups is less clear, however, it is noted that TEAEs with a fatal outcome occurred in 12 participants (12/25; 48.0%) in the originally randomised defibrotide arm and 8 participants (8/31; 25.8%) in the originally randomised best supportive care arm. No satisfying explanation for these findings has been provided.

Notably, also in the previous randomised defibrotide prophylaxis study (paediatric study 2004, assessed within the MA procedure) a higher death rate in the defibrotide arm compared to the control arm was noted. The higher death rate when children who did not develop VOD received defibrotide were compared with subjects in the control arm who did not develop VOD remained unexplained. An indication for prophylaxis of VOD was sought within the MA procedure, but the B/R was found negative based on study 2004. An extensive off-label use has been reported in previous procedures; in study DF VOD-2013-03-REG, a European observational registry study assessed within procedure EMEA/H/C/002393/II/0048, it was found that the majority of subjects included were treated with Defitelio off-label, primarily for prophylaxis of VOD (76/176 or 43%) and for non-severe VOD. Also in PSURs and in the DEFIFrance registry (final study report currently assessed within procedure EMEA/H/C/002393/II/0048), a large proportion of off-label use for prophylaxis of VOD has previously been reported.

The B/R balance of defibrotide for prevention of VOD is found clearly negative based on study 15-007. Formally, the SOB relating to this study has been fulfilled. For the safety concerns addressed by this study, overall, no firm conclusions can be drawn; however, no new safety concerns have been identified. The Rapporteur also proposes that the EPAR should be publicly available after finalisation of this procedure.

Finally, given the shown lack of efficacy for prevention of VOD and taking the established safety profile into account, the well documented off label use in the prophylactic setting (See also EMEA/H/C/002393/II/0058) raises concerns. In the previous round, the MAH was asked to submit a draft DHPC and communication plan (in line with recommendations in the GVP Module XV – Safety communication including Annex II with templates for the DHPC and Communication plan), as it was considered important to communicate directly to concerned health care professionals about these new data. In a response of 19 April 2022, the MAH has argued against the need for such communication. This was not agreed. On 28 April, the MAH submitted a draft, which has been revised and discussed at the PRAC meeting held on 2-5 May 2022. The PRAC supports a DHPC and have made comments to the drafts provided (see section 9 PRAC advice and attachments). The MAH has accepted the text after proposing some minor amendments which is now agreed by CHMP.

All current SOBs are fulfilled with this procedure and with the ongoing 8th annual reassessment procedure EMEA/H/C/002393/S/0057 (also addressing the outstanding SOB on data from the CIBMTR registry). None of the fulfilled SOBs have provided any comprehensive data and thus, no change of the exceptional circumstances status is foreseen; the proposal of a new SOB is within the scope of the annual reassessment procedure.

The benefit-risk balance of Defitelio, remains unchanged.

3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation requested		**Type**	**Annexes affected**
C.I.11.b	C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required	Type II	I, IIIA and IIIB

Submission of the final report from study 15-007 listed as a specific obligation in the Annex II of the Product Information. This is a phase 3, randomised, adaptive study (15-007) of Defibrotide vs. best supportive care in the prevention of hepatic veno-occlusive disease in adult and paediatric patients undergoing hematopoietic stem cell transplant (HSCT). The RMP version 9 has also been submitted.
The MAH has also taken the opportunity to align the PI to the latest QRD template 10.2 which replaces the United Kingdom with United Kingdom (Northern Ireland) in the PIL.
In addition, the MAH is correcting the following errata during the linguistic review of the PI: correction of the paragraph number for Regulation (EC) No 726.2004 which was cited incorrectly in Annex II of the French PI and formatting updates to Norwegian and Swedish language PIs.

☒is recommended for approval.

Annex: Rapporteur’s assessment comments on the type II variation

4. Introduction

Defitelio (defibrotide) is indicated for the treatment of severe hepatic veno-occlusive disease (VOD) also known as sinusoidal obstruction syndrome (SOS) in haematopoietic stem-cell transplantation (HSCT) therapy in adults, adolescents, children and infants over 1 month of age.

VOD/SOS belongs to a group of transplant-related, systemic endothelial diseases and is a potentially life-threatening complication of HSCT, triggered by several factors including toxicity of the conditioning regimen. The primary insult in VOD/SOS is injury to both sinusoidal endothelial cells and hepatocytes in zone 3 of the hepatic acinus, triggered by several factors including toxicity of the conditioning regimen, release of cytokines due to inflammation and engraftment, release of endotoxins, phenomena of alloreactivity, protein C anticoagulant pathway abnormalities, use of calcineurin inhibitors and monoclonal antibodies. The disease progresses with deposition of fibrinogen and factor VIII within the venular walls and liver sinusoids, venular occlusion and ultimately widespread zonal liver disruption and centrilobular haemorrhagic necrosis. In addition, a procoagulant state is often seen with low plasma levels of antithrombin, protein C and factor VII and increased levels of PAI-1 and vWF multimers (Negrin RS et al 2020). Varying incidence rates ranging from 0 to 62 percent has been reported across studies, with a two-to threefold higher incidence in children following HSCT therapy as compared to adults. In most cases, VOD/SOS resolves within weeks; however, about 50% develop renal insufficiency, and a minority progresses further to severe VOD/SOS and eventually multi-organ dysfunction/failure with a mortality rate >80%. In paediatric patients, an estimated 30-60% of affected children with VOD/SOS may progress to multi-organ dysfunction/failure.

VOD/SOS is a clinical diagnosis. There are no laboratory tests or imaging findings that are specific for VOD/SOS; serum aminotransferases and bilirubin are often increased, and markers of hepatic function often affected, such as prothrombin time. The European Society for Blood and Marrow Transplantation (EBMT) has proposed new diagnostic guidelines and prospective severity grading criteria for adults (Mohty 2016) and for children (Corbacioglu 2018). Two criteria systems have been used for definition of VOD/SOS: the modified Seattle criteria and the Baltimore criteria; however, the sensitivity and specificity of these clinical criteria have not been well defined (Negrin RS et al 2020). The adult diagnostic criteria from EBMT encompass classical VOD/SOS as defined by Baltimore criteria and also include late-onset VOD/SOS (VOD/SOS developing after 21 days post-HSCT). The new paediatric diagnostic criteria from EBMT do not require hyperbilirubinemia and do not include a defined timeframe of onset. These new diagnostic guidelines are designed to support earlier diagnosis and treatment with greater specificity, and to highlight substantial differences in presentation between adult and paediatric patients (e g, anicteric presentation in ~30% of children, which is rare in adults presenting by Day 21 post-HSCT) (Corbacioglu 2018; Mohty, 2016). With these criteria, severe VOD/SOS in adults is diagnosed according to the following (at least two criteria are required): time since first clinical symptoms of VOD/SOS =/< 4 days, bilirubin (µmol/L) between 85 and 136, bilirubin levels doubling within 48 h, transaminases more than 5 and less than 8 x UNL, weight increase between 5 and 10% and renal function impaired by more than a factor 1,5 and less than 2 as compared to at transplant. Of note, with these criteria, patients are not required to have multi-organ dysfunction/failure to be classified as 'severe' – if multi-organ failure is present, the patient is classified as very severe VOD/SOS. Also for paediatric patients, if MOD/MOF is present, the severity is graded as 'very severe'. For 'severe' VOD/SOS in paediatric patients, the following criteria are included: liver function tests > 5 x ULN, persistent refractory thrombocytopenia > 7 days, bilirubin (µmol/L) >34, ascites with necessity for paracentesis, impaired coagulation and impaired renal function with GRF (mL/min) 29-15, need for invasive pulmonary ventilation and normal CNS function (Corbacioglu 2018).

In general, mild to moderate VOD/SOS generally has a good outcome with minimal interventions, while severe VOD/SOS predicts a poor outcome and warrants more aggressive therapy. For severe VOD/SOS, defibrotide is the only approved treatment in addition to supportive care.

Defitelio (defibrotide) is a mixture of porcine polydeoxyribonucleotides which is considered to affect endothelial homeostasis. However, the mechanism of action of defibrotide is not fully understood. Defitelio was granted an MA under exceptional circumstances in 2013 after a re-examination procedure based on retrospective data and small prospective studies with historical controls, with the specific obligation (SOB) of a Post-Approval Safety Study (PASS). To fulfil the SOB, the MAH, in collaboration with the EBMT, designed a PASS (DF VOD-2013-03-REG; EMEA/H/C/002393/SOB/PR0001) for a multi-centre, multinational, prospective, noninterventional registry to record safety and outcome data in patients diagnosed with severe VOD following HSCT treated or not with Defitelio. However, this SOB could not be fulfilled as it showed not feasible to find patients for the control group. The re-classification of this study was assessed within procedure EMEA/H/C/002393/II/0027. The study protocol was amended to a single-arm, multi-centre, multinational, prospective, observational registry. Patients enrolled into the study will be followed for adverse events for 12 months and data will be collated and provided as a Category 3 PAM. Two new SOBs were agreed:

Table 1. Full list of SOBs

Number	Description	Status / Due date
Former SOB 001	Prior to launch, the Marketing Authorisation Holder (MAH) shall set up a patient registry to investigate the long-term safety, health outcomes and patterns of utilisation of defibrotide during normal use. It shall be a multi-centre, multinational and prospective observational disease registry of patients diagnosed with severe hepatic VOD following haematopoietic stem cell transplantation (HSCT) and enrol patients treated with defibrotide, other treatments or supportive care. The MAH shall ensure that information regarding all safety concerns identified in the most recent version of the Risk Management Plan is being collected. The MAH shall also ensure that all health care professionals who might prescribe defibrotide are provided with information on the importance of, and how to enter patients in, the registry.	Currently classified PAM (Cat III). **Fulfilled**
New SOB 1	In order to collect comparative safety data, the MAH will provide the final CSR and a report of comparative safety data from the Phase 3, randomised, adaptive study (15-007) of Defibrotide vs best supportive care in the prevention of hepatic veno-occlusive disease in adult and paediatric patients undergoing hematopoietic stem cell transplant (HSCT). The report will also reflect on the safety data being collected during prophylactic treatment, and any potential safety differences related to the difference in indication (ie treatment vs prophylactic therapy).	End of June 2021 **Scope of this procedure**
New SOB 2 (first part)	In order to provide comparative data on efficacy, the MAH will submit systematic literature reviews and analysis on - pooled outcomes of patients with VOD treated with defibrotide - VOD incidence and outcomes in patients not treated with defibrotide	Q2 2019 **Fulfilled**
New SOB 2 (second part)	Data analysis from CIBMTR for patients treated and not treated with Defibrotide should be provided	End of December 2021

New SOB 2 first part was assessed within procedure EMEA/H/C/002393/II/0043 and was considered formally fulfilled, although no firm conclusions on efficacy could be made.

The PAM Category III (former SOB 001) was assessed within procedure EMEA/H/C/002393/II/0048, concluding that Defitelio was used extensively off-label in that study, that clear definitions of VOD/severe VOD were missing and that there was no independent review of diagnoses, however,

there were no apparent safety signals identified. No firm conclusions on efficacy or safety could be made.

This type II variation includes the final study report for the current SOB 1, pertaining to comparative safety data from the Phase 3, randomised, adaptive study (15-007) of Defibrotide vs. best supportive care in the prevention of hepatic veno-occlusive disease in adult and paediatric patients undergoing hematopoietic stem cell transplant (HSCT), also reflecting the safety data being collected during prophylactic treatment, and any potential safety differences related to the difference in indication (ie treatment vs prophylactic therapy). *Of note, this pertains to a different indication (prevention) as compared to the approved one (treatment). Further, this study includes also efficacy data that are included in the report and are summarised below.*

5. Clinical pharmacology

5.1. Pharmacokinetics

The plasma pharmacokinetics of defibrotide was evaluated in Study 15-007 following repeated intravenous dosing (2-hour infusion) at a dose of 6.25 mg/kg given four times a day.

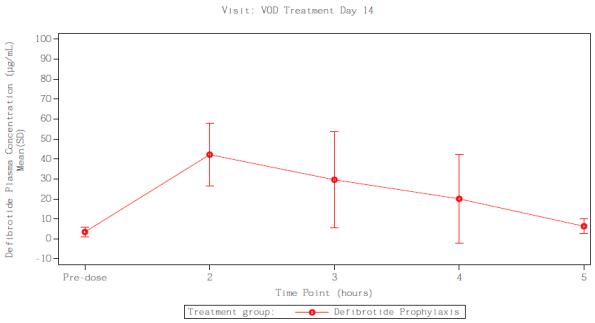
The PK evaluable analysis set included participants who have at least one evaluable PK parameter, i.e. 6 subjects in the DP arm and 16 subjects in the BSC arm. Different sampling schedules were used depending on body weight (≥30 kg or 15-30 kg), whether a subject developed VOD (and received defibrotide *rescue* treatment) or not, and depending on day post-HSCT or day of VOD treatment. Plasma concentration *versus* time data were evaluated based on non-compartmental analysis.

The majority of the PK results came from Day 14 data in patients who developed VOD and weighing ≥30 kg. In those subjects, blood samples were drawn at the following time points in relation to start of infusion: *ca* -15 min and at 2, 3, 4 and 5 hrs.

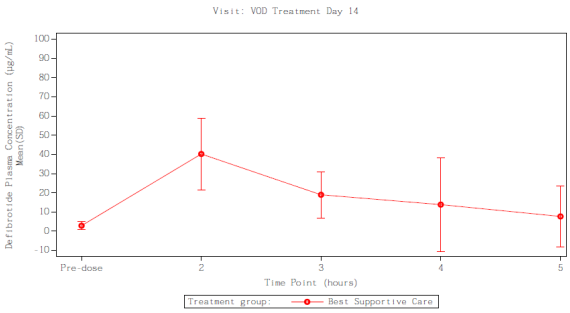
During the rescue phase on VOD treatment Day 14, the mean C_{max} and AUC_{last} were:
44.4 µg/mL and 119 h·µg/mL, respectively, in the DP arm (n=4)
39.7 µg/mL and 90.7 h·µg/mL, respectively, in the BSC arm (n=14)

The figures below show the mean defibrotide plasma profiles in the same subjects. The median half-life was 0.8 hours in both groups.

DP (n=4)



BSC (N=14)



In the DP arm of the prophylaxis phase (n=2), the mean C_{max} and AUC_{last} were:
30.4 µg/mL and 61.6 h·µg/mL, respectively, on Day +1 post-HSCT
40.0 µg/mL and 78.2 h·µg/mL, respectively, on Day +7 post-HSCT.

Sparse defibrotide plasma concentration data (mostly only at end of infusion) were obtained during the prophylaxis phase on Day 7, 15 and 30 post-HSCT, and in the rescue phase on VOD treatment Day 30. These data are stated to be intended for future population PK analysis.

Assessor's comment:

The PK results from Study 15-007 included descriptive plasma exposure parameter estimates for defibrotide in a limited number of patients, primarily those with a body weight of ≥30 kg and who developed VOD (n=4 in the DP arm and n=14 in the BSC arm). In general, peak concentrations were observed at the stop of the intravenous infusion and declined with a half-life of 0.8 hours, which is similar to that in healthy volunteers. The interindividual variability in exposure was high, for $AUC_{0\text{-}tlast}$ 60%CV.
Based on the presented results, no conclusions can be drawn regarding potential differences in the PK between age/weight groups. A valid estimate of the clearance was not obtained in the present study.

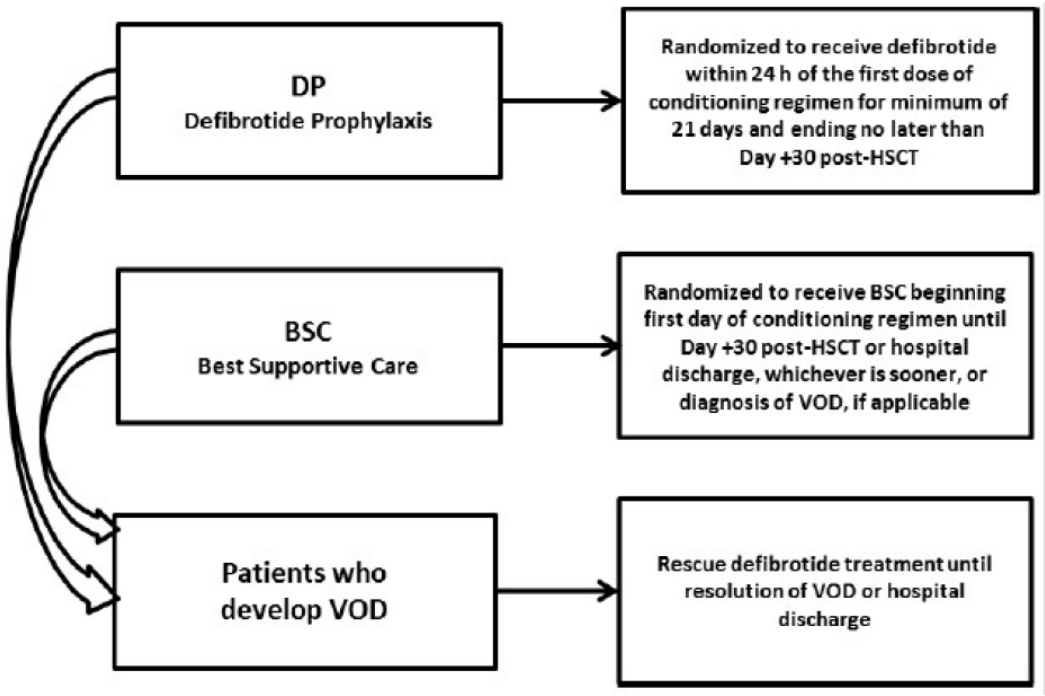
6. Clinical Efficacy aspects

6.1. Study 15-007

Overview of Study Design

Study 15-007 was a phase 3, randomized, adaptive study comparing the efficacy and safety of defibrotide vs best supportive care (BSC) in the prevention of hepatic VOD in adult and paediatric participants undergoing HSCT who were at high risk or very high risk of developing VOD, as diagnosed using the modified Seattle criteria.

Figure 1. Study Diagram



If participants in either the DP or BSC arm developed VOD, per the modified Seattle criteria, they should have received rescue defibrotide treatment for VOD as prespecified in the protocol. For participants in either arm who developed VOD, defibrotide for rescue treatment of VOD was to be administered until resolution of VOD or hospital discharge.

Participants continued to be monitored for development of late-onset VOD through Day +180 post-HSCT.

Assessor's comment:

Study 15-007 aimed at prevention of VOD, which is not an approved indication for Defitelio. However, subjects included who developed VOD would receive defibrotide as rescue treatment, which is according to the label albeit for **severe** VOD only.

The study treatment phase with defibrotide for prophylaxis of VOD was up to 30 days post-HSCT. Monitoring of late-onset VOD continued up to day 180 post-HSCT.

6.2. Methods – analysis of data submitted

Study participants

This study enrolled adult and paediatric participants (from 1 month and older) scheduled to undergo HSCT who were at high risk or very high risk of developing VOD.

Key inclusion criteria included:

• Participant must have been scheduled to undergo allogeneic (adults or paediatrics) or autologous HSCT (paediatrics only) and have been at high risk or very high risk of developing VOD.

– "High risk" was defined as participants scheduled to receive myeloablative conditioning (2 alkylating agents or at least 1 alkylating agent + total body irradiation) and who had ≥ 1 hepatic risk factor, hepatic irradiation, documented evidence of iron overload, or advanced stage neuroblastoma.

– "Very high risk" was defined as one of the following: participants who had prior treatment with an ozogamicin-containing monoclonal antibody, participants with osteopetrosis or primary immunodeficiency syndromes who must have received myeloablative conditioning (2 alkylating agents or at least 1 alkylating agent + TBI), or patients with Class III, high-risk thalassemia ≥ 7 years old with a confirmed diagnosis of hepatomegaly.

Key exclusion criteria were:

• Participant had hemodynamic instability within 24 hours before the start of study treatment.

• Participant had acute bleeding that was clinically significant (as defined in the study protocol) within 24 hours before the start of study treatment.

• Participant used any medication that increases the risk of bleeding within 24 hours before the start of study treatment.

See study protocol for detailed definitions of high risk/very high risk and full list of eligibility criteria.

Assessor's comment:

The study aimed at assessing the prophylactic effect of adding defibrotide to standard of care (best supportive care) to prevent VOD in children (>1 month) and adults who were scheduled to undergo HSCT. The study included only subjects in whom the risk of developing VOD was expected to be high or very high, based on what is currently known about the disease, mainly based on liver disease and the planned conditioning regimens. Haemodynamically unstable patients and patients with acute bleeding or recent treatment that increases the risk of bleeding were excluded. Thus, the population studied is considered suitable for assessing any prophylactic effect of defibrotide based on the assumed (very) high risk of VOD while the risk of bleeding (which is a labelled adverse reaction of defibrotide) would be low.

Treatments

Participants were randomly assigned in a 1:1 ratio to receive DP 25 mg/kg/day or BSC. All participants enrolled in the study (DP and BSC arms) were to receive individualized standard of care therapy based on local institutional guidelines and patient need. This standard of care therapy or BSC was intended to serve as a study control for comparison with those participants randomized to receive BSC plus DP.

Defibrotide solution was administered intravenously by study site personnel at a dose of 25 mg/kg/day, divided into 4 equal doses of 6.25 mg/kg/dose given as 2-hour infusions every 6 hours. The reference therapy in this study was BSC according to institutional guidelines and patient need, excluding defibrotide. Prohibited medications (ie, medications that increase the risk of bleeding) were allowed in the BSC arm, as per institutional guidelines, but not concomitantly with defibrotide while taking rescue treatment for VOD. There were no changes in the formulation manufacturing batches.

The formulation used in Study 15-007 is the same as the marketed formulation. The same formulation of defibrotide was used for adults and paediatric participants.

For participants randomized to receive defibrotide prophylaxis, 2 to 4 doses of defibrotide should have been administered within 24 hours prior to the first dose of conditioning regimen. Defibrotide administration was recommended for a minimum duration of 21 days and ending no later than Day +30 post-HSCT. Participants randomized to the BSC arm received standard of care therapy according to institutional guidelines and patient need. Administration of BSC was to begin on the first day of conditioning and continue until Day +30 post-HSCT or hospital discharge, whichever was sooner, or diagnosis of VOD, if applicable. For participants who developed VOD per modified Seattle criteria in either the DP or BSC arms, defibrotide should have been administered as treatment for VOD until resolution of VOD or hospital discharge.

If a participant on defibrotide developed bleeding, defibrotide should be discontinued. Additionally, temporary discontinuation of defibrotide was recommended for participants at significant risk of major bleeding who were receiving defibrotide (prophylactically or as rescue medication) and who underwent surgery or invasive procedures.

Assessor's comment:

Standard of care therapy was based on local institutional guidelines and patient need as judged by investigators; thus, there was no formal recommendation on best supportive care.

The defibrotide dose of 25 mg/kg/day divided into 4 equal doses is the same as the approved posology for Defitelio for treatment of severe VOD, which is to be administered for a minimum of 21 days and continued until the symptoms and signs of severe VOD resolve. Thus, the exposure to defibrotide for VOD prophylaxis in this study was similar to the label for treatment of severe VOD.

Objectives

Primary objective:

To compare the efficacy of defibrotide prophylaxis in addition to BSC (DP arm) vs BSC alone (BSC arm) for the prevention of VOD as measured by VOD-free survival by Day +30 post-HSCT in participants who were at high risk or very high risk for developing VOD.

Secondary objectives:

The key secondary objective of the study was to compare the efficacy of defibrotide prophylaxis in addition to BSC (DP arm) vs BSC alone (BSC arm) for the prevention of VOD as measured by VOD-free survival by Day +100 post-HSCT in participants who were at high risk or very high risk for developing VOD.

Other secondary objectives of the study were:

To further compare the efficacy of defibrotide prophylaxis in addition to BSC (DP arm) vs BSC alone (BSC arm) on additional variables, as follows:

- Incidence of VOD by Day +30 post- HSCT
- VOD-free survival by Day +180 post- HSCT
- NRM (non-relapse mortality) by Day +100 and by Day +180 post-HSCT

- Incidence of VOD-associated MOD (ie, severe VOD) by Day +30 and by Day +100 post-HSCT (in those participants who developed VOD)
- Proportion of participants who have resolution of VOD by Day +180 post- HSCT and time to resolution of VOD (in those participants who developed VOD)
- Incidence of VOD after Day +30 post- HSCT, by Day +100, and by Day +180 post-HSCT
- To compare the health-related quality of life using the following questionnaires:
    - 5-Level EuroQol-5D (EQ-5D-5L) (adults only)
    - EuroQol-5D for Youth (EQ-5D-Y), proxy version 1 (paediatric participants 4 to 7 years of age)
    - EQ-5D-Y, self-report version 1 (paediatric participants 8 to < 16 years of age)
- To characterize the PK of defibrotide
- To compare the overall safety of defibrotide in addition to BSC vs BSC alone, including AE profile, SAE profile, laboratory abnormalities, and vital signs (including peri-infusional vital signs for participants who received defibrotide)
- To compare the overall safety of defibrotide in addition to BSC vs BSC alone by comparing the incidence of Grades 2, 3, and 4 acute GvHD by Day +30, Day +100, and Day +180 post-HSCT, and the incidence of chronic GvHD at Day +180 post-HSCT
- To compare graft failure and time to neutrophil and platelet engraftment

The exploratory objectives of this study were as follows:

• To compare the hospital resource utilization for defibrotide prophylaxis and BSC participants

• To evaluate plasma concentration of potential predictive or prognostic VOD biomarkers (which may have included but were not limited to VCAM1, vWF, Lficolin, PAI-1, thrombomodulin, CRP, ANG2) and/or GvHD biomarkers (which may have included but were not limited to TNFR1, IL1RL1, also known as ST2, and REG3α)

• To evaluate immunogenicity of defibrotide in participants who received defibrotide for treatment or prophylaxis

Outcomes/endpoints

Primary endpoint:

- VOD-free survival rate by Day +30 post-HSCT, as adjudicated by the independent EPAC.

Analysis method: Time to event analysis of independently adjudicated results, based on combined Stage 1 and Stage 2 log rank statistics stratified by risk status and age group.

Secondary endpoints:

The key secondary efficacy objective of the study was VOD-free survival by Day +100 post-HSCT, as adjudicated by the independent EPAC.

Other secondary endpoints included:

- Incidence of VOD by Day +30 post- HSCT
- VOD-free survival by Day +180 post- HSCT
- NRM by Day +100 and by Day +180 post-HSCT
- Incidence of VOD-associated MOD (ie, severe VOD) by Day +30 and by Day +100 post-HSCT (in those participants who developed VOD)
- Proportion of participants who had resolution of VOD by Day +180 post-HSCT and time to resolution of VOD
- Incidence of VOD after Day +30 post- HSCT up to Days +100 and +180 post- HSCT
- Health-related quality of life using EQ-5D-5L (adults only), EQ-5D-Y (proxy version 1; pediatric participants 4 to 7 years of age), and EQ-5D-Y (self-report version 1; pediatric participants 8 to < 16 years of age)
- Pharmacokinetics of defibrotide
- Safety of defibrotide in addition to BSC vs BSC alone, including AE profile, SAE profile, laboratory abnormalities, and vital signs
- Incidence of Grades 2, 3, and 4 acute GvHD by Days +30, +100, and +180 post-HSCT, and the incidence of chronic GvHD by Day +180 post-HSCT
- Graft failure and time to neutrophil and platelet engraftment

Exploratory endpoints:

• Hospital resource utilization

• Evaluate plasma concentration of potential predictive or prognostic VOD biomarkers (which may have included, but were not limited to VCAM1, vWF, L-ficolin, PAI-1, thrombomodulin, CRP, ANG2) and/or GvHD biomarkers (which may have included, but were not limited to TNFR1, IL1RL1 [also known as ST2], and REG3α)

• Evaluate immunogenicity of defibrotide in participants who received defibrotide for treatment or prophylaxis (primarily presence of anti-defibrotide binding and neutralizing antibodies)

An independent EPAC that was blinded to study treatment assignment was established to determine whether a participant met the criteria for the primary efficacy endpoint (ie, VOD-free survival by Day +30 post-HSCT) and the key secondary efficacy endpoint (ie, VOD-free survival at Day +100 post-HSCT) using the modified Seattle criteria for diagnosis of VOD.

Assessor's comment:

The primary objective was to compare the efficacy of defibrotide prophylaxis in addition to BSC vs BSC alone for the prevention of VOD, with the primary endpoint VOD-free survival rate by Day +30 post-HSCT. An independent endpoint adjudication committee that was blinded to study treatment assignment determined whether criteria for the primary and key secondary efficacy endpoints were met, using modified Seattle criteria for diagnosis of VOD.

Safety outcomes were secondary; such endpoints included safety of defibrotide in addition to BSC vs BSC alone (including AE profile, SAE profile, laboratory abnormalities, and vital signs); health-related QoL; incidence of grades 2, 3 and 4 acute GvHD and incidence of chronic GvHD by Day 180 +HSCT; graft failure and time to neutrophil and platelet engraftment.

Mortality was included in the primary efficacy endpoint (VOD-free survival rate by Day +30) and the secondary endpoints VOD-free survival by Day +100 and +180 post-HSCT, and NRM (non-relapse mortality) by day 100 and 180 post-HSCT. There is also a post-hoc analysis on overall mortality, see Safety below.

Sample size

On the basis of literature and results from a previously conducted prevention study (Study 2004-000592-33) with defibrotide (Corbacioglu et al 2012), the proposed sample size was 200 patients per treatment group for a total sample size of 400 patients. Through simulations, this sample size provides a 90% power to detect a hazard ratio (HR) of 0.46 for VOD-free survival by Day +30 post-HSCT in DF group as compared with BSC group, with an average of 68 events total. The HR of 0.46 is based on 86% and 72% VOD-free survival rates by Day +30 post-HSCT for DF group and BSC group respectively, which translate to 14% and 28% as the incidence of VOD or death by Day+30 post-HSCT for the 2 groups respectively. The assumptions for the simulations to calculate the sample size also include: (1) a two-look group sequential design at one-sided significance level of 0.025 (overall) with one interim analysis for efficacy stopping (one-sided significance level of 0.0005) or non-binding futility stopping at <=10% conditional power; and (2) 10% dropout rate. Due to uncertainties associated with the study design assumptions, specifically the background rate of events in the BSC treatment group and the size of the treatment effect, an interim analysis to be overseen by the DMC was planned when 70% of patients are evaluated for the primary efficacy endpoint (i.e., VOD-free survival by Day +30 post-HSCT), with specific rules for efficacy stop (i.e., 1-sided alpha of 0.0005), futility stop (i.e., conditional power <10%), and possible sample size re-estimation up to a maximum of 600 patients total when the conditional power is in the promising zone.

The pre-planned interim analysis was conducted after 280 participants (70% of planned sample size) had been evaluated for the primary efficacy endpoint. Based on the results of the interim analysis, the DMC recommended that study enrolment be stopped based on futility. The DMC concluded that it was highly unlikely to reach statistical significance in the final analysis of the primary endpoint of VOD-free survival at Day +30 post-HSCT if the study were to complete enrolment. Screening was stopped on 29 April 2020. A total of 372 participants are included in the final study results presented.

Assessor's comment:

The study was stopped based on futility after evaluation of the pre-planned interim analysis including data from 280 subjects. Nevertheless, a total of 372 participants are included in the final study results presented, which is in line with the proposed sample size.

Randomisation

All participants were assigned to randomized study intervention using an IWRS. The investigator or designee accessed IWRS to obtain treatment assignments for participants eligible for the study. The sponsor remained blinded to the master randomization code until after database lock. Randomization was stratified according to risk of developing VOD (high risk or very high risk), age (> 16 years or ≤ 16 years), and country. If a participant met both the high-risk and the very high-risk criteria, the participant was classified as very high risk.

Assessor's comment:

Randomisation was stratified according to age, country and risk of developing VOD (high-risk or very high-risk) with enrolment of participants meeting high-risk criteria capped at 65% of the total enrolment.

Blinding (masking)

This was an open-label study.

To minimize potential for bias, the following blinding measures were employed:

• The central reviewer of imaging studies was blinded to study treatment assignment and all non-radiologic participant data.

• Members of the EPAC were blinded to study treatment assignment, were not employees of the sponsor, and were not otherwise involved in the study.

• The sponsor did not have access to the assessment of VOD by the EPAC for analysis of the primary endpoint. In addition, the sponsor was blinded to the DMC reports/outputs produced independently for the closed sessions of the DMC meetings throughout the study until the database lock and unblinding.

Assessor's comment:

The study was open-label, but assessment of the primary efficacy outcome events was done by a blinded endpoint-adjudication committee. This is of some interest given the large discrepancy between investigators assessment and EPAC assessment of VOD (see Outcomes below).

Statistical methods

The analyses for the primary and key secondary endpoints of VOD-free survival by Day +30 and Day +100, respectively, were based on EPAC adjudication of VOD. Sensitivity analyses to evaluate the robustness of the primary analysis were also based on EPAC adjudication. A descriptive analysis was performed on the investigator assessment of VOD to assess consistency between investigator and EPAC results.

To control the study-wise type I error, a sequential testing strategy began with the test of the primary efficacy endpoint. The test on the key secondary efficacy endpoint was only to be conducted if the primary efficacy endpoint was statistically significant. This gate-keeping approach kept the family-wise error rate at 1-sided 0.025 for the comparisons of the 2 treatment arms in the primary and the key secondary efficacy endpoint analyses. Other secondary efficacy endpoints were descriptive and tested without multiplicity adjustments; p-values are nominal.

Primary Efficacy Endpoint and Analysis

The primary efficacy analysis was to be performed using the ITT population. The primary efficacy endpoint was the VOD-free survival rate by Day +30 post-HSCT, as adjudicated by the independent EPAC. Kaplan-Meier estimates of the VOD-free survival rate by Day +30 post-HSCT were to be presented for the 2 treatment groups and a stratified log rank test was to be performed as the primary efficacy endpoint analysis to establish the treatment difference. In addition, as a sensitivity analysis, the Cochran-Mantel-Haenszel test would be used to compare a composite binary endpoint of VOD free + alive at Day +30 post-HSCT between the 2 treatment groups, where the composite binary endpoint is defined by the proportion of patients who are VOD free and alive at Day +30 post-HSCT.

Additional sensitivity analyses for the primary efficacy endpoint included but were not limited to: the unstratified log rank test for the ITT population and the stratified log rank test using the mITT population. Both the stratified log rank test and the CMH test were to be performed by the 2 stratification variables for randomization - very high risk/high risk and paediatric (≤ 16 yrs)/adults (>16 yrs).

The timing variable for the primary efficacy endpoint was anchored at time of HSCT (time=0). It was anticipated that fewer than 2% of patients would not undergo HSCT in the ITT population. For those patients, time 0 is counted at randomization. The timing variable was defined as the number of days from time 0 to the earlier of VOD or death by Day +30. If a patient was not followed for 30 days, the censoring for that endpoint would be defined at the time of last available evaluation of VOD by EPAC. If a patient in BSC group was rescued but VOD is not confirmed by EPAC then the patient will be censored at the time of rescue initiation. Additional analysis based on other timing and censoring strategies would be considered and detailed in the SAP.

Patients assessed for the primary efficacy endpoint before the interim analysis make up the stage 1 sample, and those patients assessed after the interim analysis make up the stage 2 sample. At interim analysis, the stage 1 sample was used to construct the treatment difference of the primary efficacy endpoint and the stratified log rank test of efficacy. For the final analysis, the method of Cui, Hung, and Wang (Cui et al 1999) was to be used to combine the independent stratified log rank test statistics from stage 1 and stage 2. To maintain an overall significance level at 1-sided alpha=0.025, the incremental alpha is specified at 1-sided 0.0005 for interim analysis and 1-sided 0.0245 for final analysis (the corresponding nominal 1-sided alpha is 0.0005 for interim analysis and 1-sided 0.02498 for final analysis).

Secondary Efficacy Endpoint and Analysis

The key secondary efficacy endpoint is VOD-free survival by Day +100 post-HSCT and was to be analysed similarly to the primary efficacy endpoint. The remaining secondary efficacy endpoints were to be tested without multiplicity adjustments, and nominal p-values would be reported.

The incidence of NRM by Day +100 and Day +100 post-HSCT was compared between the treatment arms. Non-relapse mortality was defined as death that occurs after HSCT in participants who were noted as having malignant primary disease on the disease history eCRF and who did not have primary disease relapse post-HSCT. Only participants with malignant primary disease at baseline were included in the analysis.

For Resolution of VOD and Time to Resolution of VOD, of those patients who were diagnosed with VOD by Day +30 post-HSCT by the investigator, the proportion of patients who have resolution of VOD by Day +180 post-HSCT would be summarized by treatment group. The time to resolution of VOD was defined as the date of VOD diagnosis to the date that the last criterion for resolution of VOD was met. Time to resolution of VOD was to be summarized and compared between the 2 treatment groups using a log-rank test.

An interim analysis overseen by the DMC was planned for when 70% of participants were evaluated for the primary efficacy endpoint (ie, VOD-free survival by Day +30 post-HSCT), with specific rules for efficacy stop (ie, 1-sided alpha of 0.0005), futility stop (ie, conditional power < 10%), and possible sample size re-estimation up to a maximum of 600 participants total. Details of the interim analysis and adaptive design decision rules are provided in the interim SAP.

Changes in Planned Analyses Prior to Unblinding or Database Lock

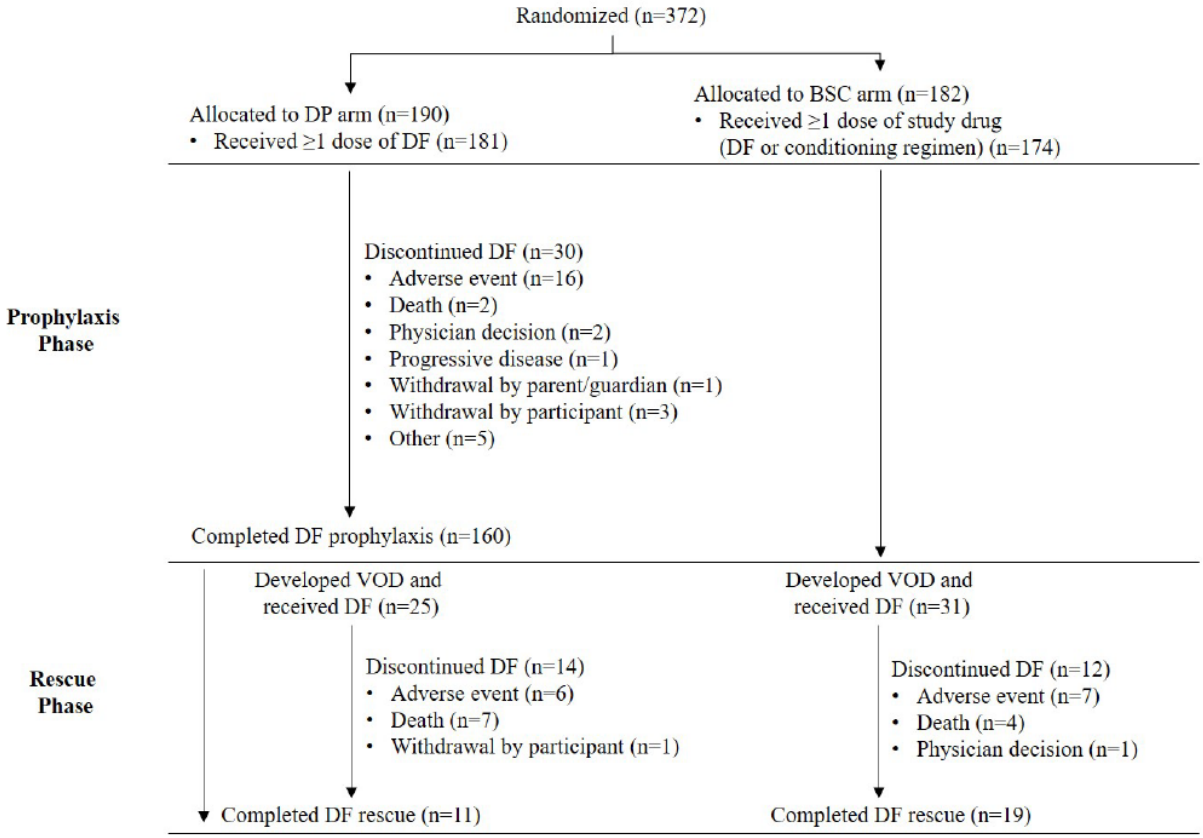
All changes in the original planned analyses for the study were implemented by a SAP amendment before unblinding and database lock (SAP Section 8.8.6). The SAP amendment includes details regarding COVID-19-related changes. The definition of the Safety Analysis Set was updated for the BSC arm to include all participants randomized who received at least 1 dose of study drug (defibrotide or conditioning regimen) to ensure that safety data would be summarized consistently in the 2 treatment arms.

Changes Following Study Unblinding/Database Lock and Post-hoc Analyses

Participants within the study may have died outside of the protocol-defined AE reporting period (see Section 6.8.1.5, Adverse Event Recording and Reporting, of the study protocol [Section 8.1.6]). Death data and cause of death throughout the entire study were captured on the Death eCRF. After database lock, a summary of all deaths by Day +30, Day +100, and Day +180 post-HSCT by treatment arm (Table 19) and a listing of all deaths by participant (Listing 16.2.21) were produced. These data are described below.

6.3. Results

Participant flow



Abbreviations: BSC = Best Supportive Care; DF = defibrotide; DP = Defibrotide Prophylaxis.
Source: Tables 14.1.2.1, 14.1.2.2, and 14.1.2.3

Assessor's comment:

There were 372 randomised subjects: 190 allocated to defibrotide in addition to best supportive care (BSC), 182 allocated to (BSC) only. During the prophylaxis phase, 30/190 (15.7%) discontinued defibrotide, the majority due to adverse events. There were 56 subjects who developed VOD and received defibrotide as rescue treatment (however, based on outcome data, there appears to have been 29 additional subjects who developed VOD – see Outcomes below). Of those who received defibrotide as rescue treatment, 26/56 discontinued treatment, the majority due to adverse events or death.

Recruitment

The study was initiated 11 January 2017. Last participant last visit was 20 October 2020. The study enrolled participants at 104 centres in Australia, Belgium, Canada, France, Germany, Israel, Italy, Japan, New Zealand, South Korea, Spain, Turkey, the United Kingdom, and the United States.

Based on the results of the interim analysis, the DMC recommended that study enrolment be stopped based on futility. The DMC concluded that it was unlikely to reach statistical significance in the final analysis of the primary endpoint of VOD-free survival at Day +30 post-HSCT if the study were to

complete enrolment. The DMC indicated no safety concerns for enrolled participants related to stopping enrolment. Screening was stopped on 29 April 2020. Participants in screening at this time discontinued all screening activities. Participants randomized to the DP or BSC arms could continue all study activities and follow-up evaluations until study completion or early termination. Because defibrotide is approved for the treatment of adult and paediatric patients with VOD, participants who were receiving VOD rescue treatment at the time enrolment was stopped could continue treatment per protocol and could continue all study activities and follow-up evaluations until study completion or early termination. Participants who developed VOD were offered defibrotide as rescue treatment per protocol and could continue all study activities and follow-up evaluations until study completion or early termination.

Conduct of the study

The **original protocol** is dated 09 May 2016. There were three amendments; Amendment 01 v2.0:19 January 2017; Amendment 02 v3.0 24 February 2017; Amendment 03 v4.0 20 August 2018.

Some more significant changes that are included in **Amendment 1 and 2** were eligibility criteria (to clarify that patients must meet to be at "high risk" or "very high risk" for developing VOD); weight criteria for PK assessments; clarifications on best supportive care, the different time periods of the study and the timing of the various assessment; that defibrotide was to be discontinued for patients who develop bleeding and that defibrotide be temporarily discontinued in patients who undergo surgery or invasive procedures at significant risk of major bleeding; dosing clarification; clarification on permitted and prohibited medications; definitions of the primary efficacy assessment regarding ascites; clarifications on adjudication/definitions for secondary efficacy assessments.

Some more significant changes that are included in **Amendment 3** were updated/revised inclusion criteria in order to clarify operational definitions of iron overload, myeloablative conditioning, and hepatomegaly, and clarification on definition of myeloablative conditioning for very high risk patients; clarifications on defibrotide dosing and when agents that increase the risk of bleeding are allowed or prohibited; revised timing of blood sample collection for pharmacokinetic assessments according to intensive schedule, sparse schedule, and contingent schedule for clarity; updated collection of concomitant medication in order to specify that all medications and therapies taken between baseline and Day +60 post-HSCT will be recorded as concomitant medications; clarification that overdose, medication errors, and drug misuse of the study drug should be reported.

Assessor's comment:

The more substantial Amendments 1 and 2 were included early in the study and are not considered to affect the overall study results. Amendment 3 was included relatively late in the study but is not found to affect the overall study results.

Baseline data

Median (min, max) age at screening overall was 14.0 (0, 72) years. The most common primary diseases in the overall study population (n=372) were acute lymphoblastic leukaemia (100 participants [26.9%]), acute myelogenous leukaemia (96 participants [25.8%]), and neuroblastoma (57 participants [15.3%]). The majority of participants had previously been treated with chemotherapy alone (101 participants [27.2%]) or chemotherapy and another treatment modality for their primary disease.

Table 1. Demographic and Baseline Characteristics – ITT Analysis Set

Variable, Statistic	DP (N=190)	BSC (N=182)	Total (N=372)
Sex, n (%)			
n	190	182	372
Male	100 (52.6)	100 (54.9)	200 (53.8)
Female	90 (47.4)	82 (45.1)	172 (46.2)
Race, n (%)			
n	190	182	372
American Indian or Alaska Native	0	0	0
Asian	39 (20.5)	46 (25.3)	85 (22.8)
Black or African American	5 (2.6)	8 (4.4)	13 (3.5)
Native Hawaiian or Other Pacific Islander	0	2 (1.1)	2 (0.5)
White	125 (65.8)	109 (59.9)	234 (62.9)
Multiple	2 (1.1)	0	2 (0.5)
Not reported	19 (10.0)	17 (9.3)	36 (9.7)
Ethnicity, n (%)			
n	190	182	372
Hispanic or Latino	22 (11.6)	21 (11.5)	43 (11.6)
Not Hispanic or Latino	150 (78.9)	143 (78.6)	293 (78.8)
Not reported	18 (9.5)	17 (9.3)	35 (9.4)
Unknown	0	1 (0.5)	1 (0.3)
Age at screening in years			
n	190	182	372
Mean (SD)	22.7 (21.87)	23.2 (21.73)	23.0 (21.77)
Median	13.0	15.0	14.0
Min; Max	0; 72	0; 69	0; 72

Variable, Statistic	DP (N=190)	BSC (N=182)	Total (N=372)
Baseline BMI (kg/m²)			
n	181	178	359
Mean (SD)	20.66 (5.502)	21.02 (5.944)	20.84 (5.720)
Median	19.44	19.67	19.55
Min; Max	12.0; 41.1	10.3; 40.2	10.3; 41.1
Primary disease, n (%)			
Acute lymphoblastic leukemia	49 (25.8)	51 (28.0)	100 (26.9)
Acute myelogenous leukemia	52 (27.4)	44 (24.2)	96 (25.8)
Chronic myelogenous leukemia	3 (1.6)	1 (0.5)	4 (1.1)
Class III thalassemia	3 (1.6)	5 (2.7)	8 (2.2)
Familial hemophagocytic lymphohistiocytosis	6 (3.2)	4 (2.2)	10 (2.7)
Griscelli syndrome II	0	1 (0.5)	1 (0.3)
Hodgkin's lymphoma	2 (1.1)	0	2 (0.5)
Multiple myeloma	0	1 (0.5)	1 (0.3)
Myelodysplastic syndrome	4 (2.1)	8 (4.4)	12 (3.2)
Neuroblastoma	27 (14.2)	30 (16.5)	57 (15.3)
Non-Hodgkin's lymphoma	7 (3.7)	2 (1.1)	9 (2.4)
Osteopetrosis	11 (5.8)	14 (7.7)	25 (6.7)
Primary hemophagocytic lymphohistiocytosis	3 (1.6)	3 (1.6)	6 (1.6)
Soft tissue sarcoma	0	1 (0.5)	1 (0.3)
X-linked lymphoproliferative disorder	0	3 (1.6)	3 (0.8)
X-linked severe combined immunodeficiency disease	1 (0.5)	0	1 (0.3)
Other	21 (11.1)	14 (7.7)	35 (9.4)
Time since initial diagnosis (days)			
n	149	142	291
Mean (SD)	514.0 (676.44)	478.1 (579.40)	496.4 (630.13)
Median	251.0	248.0	251.0
Min; Max	25; 4336	49; 3757	25; 4336
Number of recurrences for primary disease			
n	75	78	153
Mean (SD)	1.5 (0.74)	1.4 (0.60)	1.4 (0.68)
Median	1.0	1.0	1.0
Min; Max	1; 5	1; 3	1; 5

Variable, Statistic	DP (N=190)	BSC (N=182)	Total (N=372)
Prior treatment for primary diagnosis, n (%)			
Chemotherapy	54 (28.4)	47 (25.8)	101 (27.2)
Chemotherapy; HSCT	9 (4.7)	13 (7.1)	22 (5.9)
Chemotherapy; HSCT; Immunotherapy	1 (0.5)	0	1 (0.3)
Chemotherapy; HSCT; Immunotherapy; Radiation	1 (0.5)	0	1 (0.3)
Chemotherapy; HSCT; Radiation	5 (2.6)	5 (2.7)	10 (2.7)
Chemotherapy; HSCT; Radiation; Other	1 (0.5)	0	1 (0.3)
Chemotherapy; HSCT; Radiation; Surgery	0	2 (1.1)	2 (0.5)
Chemotherapy; HSCT; Surgery	1 (0.5)	0	1 (0.3)
Chemotherapy; Immunotherapy	7 (3.7)	7 (3.8)	14 (3.8)
Chemotherapy; Immunotherapy; Other	2 (1.1)	1 (0.5)	3 (0.8)
Chemotherapy; Immunotherapy; Radiation	0	1 (0.5)	1 (0.3)
Chemotherapy; Other	1 (0.5)	2 (1.1)	3 (0.8)
Chemotherapy; Radiation	5 (2.6)	3 (1.6)	8 (2.2)
Chemotherapy; Surgery	3 (1.6)	2 (1.1)	5 (1.3)
HSCT	1 (0.5)	1 (0.5)	2 (0.5)
HSCT; Immunotherapy	0	1 (0.5)	1 (0.3)
Immunotherapy	6 (3.2)	5 (2.7)	11 (3.0)
Other	1 (0.5)	2 (1.1)	3 (0.8)
Radiation; Surgery	0	1 (0.5)	1 (0.3)
Surgery	0	1 (0.5)	1 (0.3)

Abbreviations: BMI = body mass index; BSC = Best Supportive Care; DP = Defibrotide Prophylaxis; HSCT = hematopoietic stem cell transplant; ITT = Intent-to-Treat; Max = maximum; Min = minimum.
Notes: Percentages were calculated with the number of participants in each arm from the ITT Analysis Set as a denominator.
Source: Table 14.1.4.1

Transplant characteristics by treatment arm:

Table 2. Transplant Characteristics – ITT Analysis Set

Variable Statistic	DP (N=190)	BSC (N=182)	Total (N=372)
Type of graft, n (%)			
N	179	174	353
Allogenic: haploidentical (half-matched)	25 (13.2)	34 (18.7)	59 (15.9)
Allogenic: matching sibling	42 (22.1)	34 (18.7)	76 (20.4)
Allogenic: matched unrelated	54 (28.4)	49 (26.9)	103 (27.7)
Allogenic: mismatched related	5 (2.6)	3 (1.6)	8 (2.2)
Allogenic: mismatched unrelated	19 (10.0)	22 (12.1)	41 (11.0)
Autologous	32 (16.8)	32 (17.6)	64 (17.2)
Other	2 (1.1)	0	2 (0.5)
Source of graft, n (%)			
N	179	174	353
Peripheral blood stem cells	109 (57.4)	121 (66.5)	230 (61.8)
Bone marrow	52 (27.4)	39 (21.4)	91 (24.5)
Umbilical cord blood	15 (7.9)	13 (7.1)	28 (7.5)
Other	3 (1.6)	1 (0.5)	4 (1.1)
Type of conditioning regimen, n (%)			
N	180	174	354
Myeloablative	123 (64.7)	119 (65.4)	242 (65.1)
Non-myeloablative	5 (2.6)	3 (1.6)	8 (2.2)
Reduced intensity chemistry (RIC)	10 (5.3)	7 (3.8)	17 (4.6)
Other	42 (22.1)	45 (24.7)	87 (23.4)

Abbreviations: BSC = Best Supportive Care; DP = Defibrotide Prophylaxis; ITT = Intent-to-Treat.
Notes: Percentages were calculated with the number of participants in each arm from the ITT Analysis Set as a denominator. If a participant had multiple 'types of graft', 'source of graft', or 'degree of matching' records, it was assigned to 'Other' category for each variable.
Source: Table 14.1.5

There were 198 paediatric subjects (source CSR Table 14.1.4.3), with a median age of 4.5 yrs (range 0-16 yrs) at screening; 104 in the defibrotide group and 94 in the SoC group. (Selected) baseline characteristics of paediatric subjects:

Table 3 Demographic and Baseline Characteristics - Paediatric Subgroup, ITT Analysis Set

Variable, Statistic	DP (N=104)	BSC (N=94)	Total (N=198)
Primary Disease, n (%)			
Acute lymphoblastic leukemia (ALL)	18 (17.3)	16 (17.0)	34 (17.2)
Acute myelogenous leukemia (AML)	17 (16.3)	13 (13.8)	30 (15.2)
Class III Thalassemia	3 (2.9)	3 (3.2)	6 (3.0)
Familial hemophagocytic lymphohistiocytosis	6 (5.8)	4 (4.3)	10 (5.1)
Griscelli Syndrome II	0	1 (1.1)	1 (0.5)
Hodgkin's lymphoma	2 (1.9)	0	2 (1.0)
Myelodysplastic syndrome	1 (1.0)	0	1 (0.5)
Neuroblastoma	27 (26.0)	29 (30.9)	56 (28.3)
Non-Hodgkin's lymphoma (NHL)	0	1 (1.1)	1 (0.5)
Osteopetrosis	11 (10.6)	14 (14.9)	25 (12.6)
Primary Hemophagocytic Lymphohistiocytosis	3 (2.9)	2 (2.1)	5 (2.5)
Soft Tissue Sarcoma	0	1 (1.1)	1 (0.5)
X-linked lymphoproliferative disorder	0	3 (3.2)	3 (1.5)
X-linked Severe Combined Immunodeficiency Disease (SCID)	1 (1.0)	0	1 (0.5)
Other	15 (14.4)	7 (7.4)	22 (11.1)
Time Since Initial Diagnosis (Days)			
n	88	78	166
Mean (SD)	493.6 (656.41)	461.1 (571.90)	478.4 (616.51)
Median	230.0	249.0	232.0
Min ; Max	25 ; 3499	49 ; 2807	25 ; 3499
Number of Recurrences for Primary Disease			
n	32	27	59
Mean (SD)	1.5 (0.67)	1.4 (0.64)	1.5 (0.65)
Median	1.0	1.0	1.0
Min ; Max	1 ; 3	1 ; 3	1 ; 3
Prior Treatment for Primary Diagnosis, n (%)			
Chemotherapy	23 (22.1)	16 (17.0)	39 (19.7)
Chemotherapy; HSCT	5 (4.8)	5 (5.3)	10 (5.1)
Chemotherapy; HSCT; Immunotherapy; Radiation	1 (1.0)	0	1 (0.5)
Chemotherapy; HSCT; Radiation	2 (1.9)	2 (2.1)	4 (2.0)
Chemotherapy; HSCT; Radiation; Surgery	0	1 (1.1)	1 (0.5)
Chemotherapy; HSCT; Surgery	1 (1.0)	0	1 (0.5)
Chemotherapy; Immunotherapy	2 (1.9)	2 (2.1)	4 (2.0)
Chemotherapy; Immunotherapy; Other	1 (1.0)	1 (1.1)	2 (1.0)
Chemotherapy; Other	0	1 (1.1)	1 (0.5)
Chemotherapy; Radiation	4 (3.8)	2 (2.1)	6 (3.0)
Chemotherapy; Surgery	2 (1.9)	2 (2.1)	4 (2.0)
HSCT	1 (1.0)	0	1 (0.5)
Immunotherapy	3 (2.9)	2 (2.1)	5 (2.5)
Other	1 (1.0)	1 (1.1)	2 (1.0)
Surgery	0	1 (1.1)	1 (0.5)

DP = Defibrotide Prophylaxis; BSC = Best Supportive Care
[1] Percentages were calculated with the number of subjects in each arm from the ITT Analysis Set as a denominator.
Source Listing: 16.2.3.1

Assessor's comment:

For the entire study population, demographics and baseline characteristics were similar in the two treatment arms. The most frequent underlying disease was acute lymphoblastic leukaemia (100 participants [26.9%]), acute myelogenous leukaemia (96 participants [25.8%]), and neuroblastoma (57 participants [15.3%]). Transplant data for the 353/372 subjects who underwent HSCT have been provided; the majority of these had allogenic grafts. Myeloablative conditioning was given to approximately two thirds of subjects.

There were 198 paediatric subjects in the study, thus constituting more than half of the study population, with a median age of 4.5 yrs (range 0-16 yrs) at screening; 104 in the defibrotide group and 94 in the SoC group. Neuroblastoma was the most common primary disease followed by ALL and AML in the paediatric group. For 59/198 children, the primary disease was recurrent at baseline.

Numbers analysed

Analysis Set	DP	BSC	Total
Screened[a], n	190	182	372
Randomized, n	190	182	372
ITT[b], n	190	182	372
mITT[c], n	179	174	353
Safety[d], n	181	174	355
PK Analysis Set[e], n	106	16	122
PK Evaluable Analysis Set[f], n	6	16	22

Abbreviations: BSC = Best Supportive Care; DP = Defibrotide Prophylaxis; HSCT = hematopoietic stem cell transplant; ITT = Intent-to-Treat; mITT = Modified Intent-to-Treat; PK = pharmacokinetics.

[a] The Screened Analysis Set includes all participants who provided written informed consent and who undergo study screening procedures.

[b] The ITT Analysis Set includes all randomized participants.

[c] The mITT Analysis Set includes all participants in the ITT Analysis Set who underwent HSCT.

[d] The Safety Analysis Set includes all participants randomized to the DP arm who received at least 1 dose of defibrotide and all participants randomized to the BSC arm who received at least 1 dose of study drug (defibrotide or conditioning regimen).

[e] The PK Analysis Set includes all participants who received at least one dose of defibrotide and had at least one concentration sample taken.

[f] The PK Evaluable Analysis Set includes all participants in the PK Analysis Set who have at least one evaluable PK parameter.

Source: Table 14.1.1.1

Of the 372 participants randomized in the study, 241 participants (64.8%) completed the study. The most common reasons for withdrawing from the study were death (50 participants [13.4%] total) and AE (26 participants [7.0%] total).

Table 4. Participant Disposition – ITT Analysis Set

Status, n (%)	DP (N=190)	BSC (N=182)	Total (N=372)
Completed study	120 (63.2)	121 (66.5)	241 (64.8)
Withdrew from the study	70 (36.8)	61 (33.5)	131 (35.2)
Reason for withdrawing from the study			
Adverse event	13 (6.8)	13 (7.1)	26 (7.0)
Death[a]	30 (15.8)	20 (11.0)	50 (13.4)
Disease relapse	9 (4.7)	6 (3.3)	15 (4.0)
Non-compliance with study drug	0	0	0
Physician decision	7 (3.7)	6 (3.3)	13 (3.5)
Pregnancy	0	0	0
Protocol deviation	0	1 (0.5)	1 (0.3)
Screen failure	2 (1.1)	1 (0.5)	3 (0.8)
Site terminated by sponsor	0	0	0
Study terminated by sponsor	0	0	0
Withdrawal by parent/guardian	2 (1.1)	7 (3.8)	9 (2.4)
Withdrawal by participant	5 (2.6)	3 (1.6)	8 (2.2)
Other[b]	2 (1.1)	4 (2.2)	6 (1.6)

Abbreviations: BSC = Best Supportive Care; DP = Defibrotide Prophylaxis; eCRF = electronic case report form; ITT = Intent-to-Treat.

Note: Percentages were calculated with the number of participants in each arm from ITT Analysis Set as a denominator.

[a] The primary reason for withdrawing from the study was captured as death on the End-of-Study eCRF. However, survival data were collected on the Death eCRF page, and presented by participant in Listing 16.2.2.1. An ad hoc summary of these data is presented in Section 5.8.

[b] Other reasons for withdrawing from the study include: lost to follow-up (n=2), participant transferred to another treatment center (n=2), early recovery (n=1), and enrolled in another investigational study (n=1) (Listing 16.2.2.1).

Source: Table 14.1.2.1

Of the 190 participants randomized to the DP arm, 181 participants (95.3%) received at least 1 dose of defibrotide during the prophylaxis phase. The prophylaxis phase of the study is defined as follows: • If VOD occurs, the prophylaxis phase starts on the Baseline date and ends on the day before the start date of rescue defibrotide (ie, rescue treatment start date – 1). • If VOD does not occur, the prophylaxis phase starts on the Baseline date and ends on the date of study completion/early termination.

A total of 56 participants (15.1%), 25 participants (13.2%) in the DP arm and 31 participants (17.0%) in the BSC arm, experienced VOD (as diagnosed by the investigator) and received defibrotide as rescue therapy. The rescue phase is defined as follows: • For the subset of participants who developed VOD and received rescue defibrotide, the rescue treatment phase begins on the start date of rescue defibrotide and ends on the date of study completion/early termination.

Protocol Deviations

A total of 123 participants (33.1%) had a major protocol deviation, with a similar proportion of participants in each treatment arm:

Table 5. Major Protocol Deviations – ITT Analysis Set

	DP (N=190)	BSC (N=182)	Total (N=372)
Participants with major protocol deviations, n (%)	64 (33.7)	59 (32.4)	123 (33.1)
Major deviation term			
Study procedures/assessments	26 (13.7)	28 (15.4)	54 (14.5)
ICF process/timing	14 (7.4)	18 (9.9)	32 (8.6)
Study treatment admin/dispense	14 (7.4)	4 (2.2)	18 (4.8)
Informed consent	8 (4.2)	9 (4.9)	17 (4.6)
Concomitant medication	8 (4.2)	4 (2.2)	12 (3.2)
Inclusion criteria	6 (3.2)	6 (3.3)	12 (3.2)
Other GCP deviation	3 (1.6)	3 (1.6)	6 (1.6)
Exclusion criteria	2 (1.1)	0	2 (0.5)
Inv oversight	0	1 (0.5)	1 (0.3)
Inv record keeping source docs	1 (0.5)	0	1 (0.3)
Study treatment compliance	1 (0.5)	0	1 (0.3)
Study treatment randomization	1 (0.5)	0	1 (0.3)

Abbreviations: BSC = Best Supportive Care; DP = Defibrotide Prophylaxis; GCP = Good Clinical Practice; ICF = informed consent form; Inv = investigator; ITT = Intent-to-Treat.
Notes: Percentages were calculated with the number of participants in each arm from the ITT Analysis Set as a denominator. Terms were sorted by decreasing order of total frequency.
Source: Table 14.1.3

Assessor's comment:

One third of the ITT population had major protocol deviations, primarily related to study procedures/assessments (not further specified) and informed consent form processing/timing. The MAH should provide the most frequent reasons for deviation in study procedures/assessments and discuss the integrity of the study given the large number of major protocol deviations (**LoQ**).

Outcomes and estimation

Primary Efficacy Endpoint

The results of the primary efficacy endpoint, VOD-free survival rate by Day +30 post-HSCT as adjudicated by the independent EPAC, are shown in Table 6. Primary Efficacy Endpoint: VOD-free Survival by Day +30 post-HSCT – ITT Analysis Set The VOD-free survival rates at Day +30 post-HSCT in the DP arm vs the BSC arm with KM VOD-free survival estimates (95% CIs) of 66.8% (57.8%, 74.4%) and 72.5% (62.3%, 80.4%), respectively. The p-value from the stratified log rank test that compares VOD-free survival over time between the 2 treatment arms is 0.8504, indicating no difference. The HR of the DP arm with respect to the BSC arm is 1.273, with a 95% CI of 0.839 to 1.932.

Table 6. Primary Efficacy Endpoint: VOD-free Survival by Day +30 post-HSCT – ITT Analysis Set

Variable, Statistic	DP (N=190)	BSC (N=182)	DP vs. BSC
Number of participants, n (%)[a]			
VOD/death by Day +30 post-HSCT	50 (26.3)	40 (22.0)	-
Censored	140 (73.7)	142 (78.0)	
No VOD/death by Day +30 post-HSCT	112 (58.9)	113 (62.1)	
Other reason	28 (14.7)	29 (15.9)	
Stage 1 independent stratified log rank statistic	-		-1.9152
Stage 2 independent stratified log rank statistic	-		1.0304
Final log rank statistic (Stage 1 and Stage 2 combined)	-		-1.0381
P-value[b]	-		0.8504
KM estimate of median time to VOD/death in days (95% CI)	NE	NE	-
KM estimate (%) of VOD-free survival rate at Day +30 post-HSCT (95% CI)	66.8 (57.8, 74.4)	72.5 (62.3, 80.4)	
Hazard ratio (95% CI)[c]	-		1.273 (0.839, 1.932)

Abbreviations: BSC = Best Supportive Care; CI = confidence interval; DP = Defibrotide Prophylaxis; HSCT = hematopoietic stem cell transplant; ITT = Intent-to-Treat; KM = Kaplan-Meier; NE = not estimable; VOD = veno-occlusive disease.

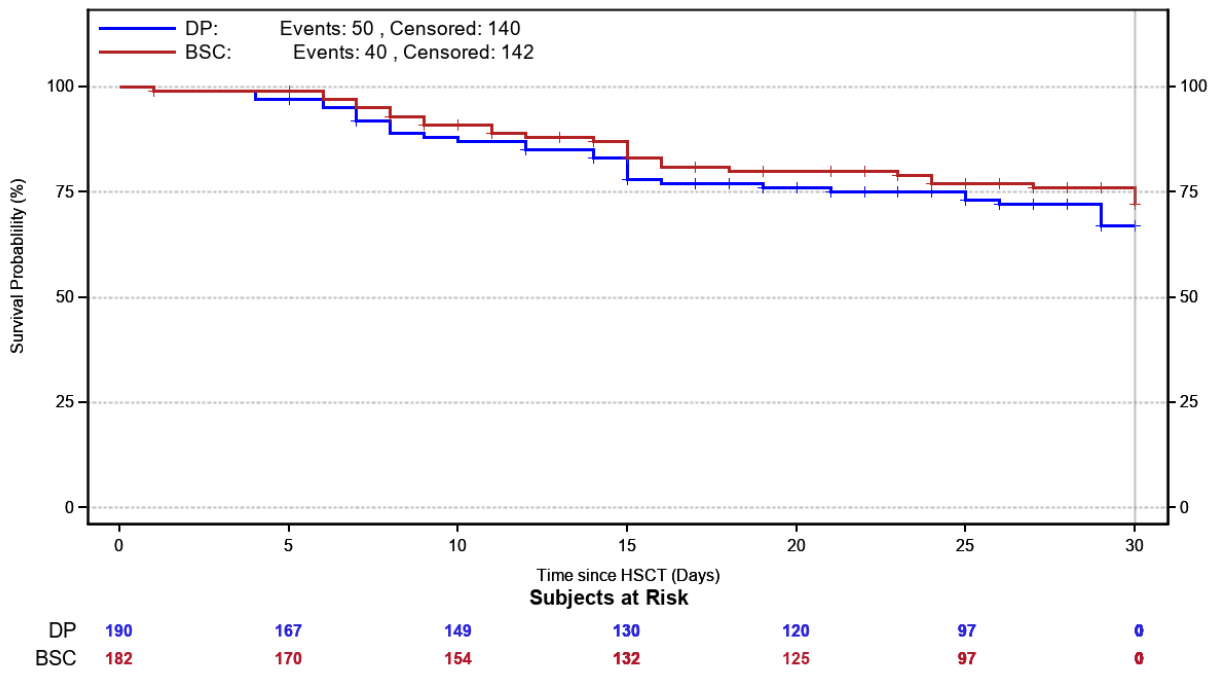
[a] Percentages were calculated with the number of participants in each arm from the ITT Analysis Set as a denominator.

[b] P-value was calculated for the combined Stage 1 and Stage 2 log rank statistics stratified by risk status and age group using the method described by Cui, Hung, and Wang (Cui 1999).

[c] The hazard ratio was from a Cox proportional hazards regression model stratified by risk status and age group.

Source: Table 14.2.1.1

Figure 2. VOD-free Survival by Day +30 post-HSCT (Primary Efficacy Endpoint): KM Plot with Number of Participants at Risk – ITT Analysis Set



Sensitivity Analyses

Sensitivity analyses were performed to address missing data, as well as to explore modifications to the definition of the primary endpoint and analysis population). Each of these sensitivity analyses are described in Section 10.1.1 of the SAP (Section 8.8.6), and results are summarized in

Table 7 Sensitivity Analyses of the Primary **Endpoint**.

Table 7 Sensitivity Analyses of the Primary Endpoint

Analysis	KM Estimate (95% CI) of VOD-free Survival Rate at Day +30 post-HSCT	
	DP	BSC
Sensitivity Analysis I (if early termination, lost to follow-up, or assessed as 'Not Evaluable' by the EPAC with the last assessment for evaluation of VOD less than Day +23 post-HSCT, participant is considered to have an event in the DP arm and is censored in the BSC arm)	53.6% (45.2%, 61.3%)	72.5% (62.3%, 80.4%)
Sensitivity Analysis III (unstratified log rank test)	66.8% (57.8%, 74.4%)	72.5% (62.3%, 80.4%)
Sensitivity Analysis IV (mITT Analysis Set)	66.8% (57.7%, 74.4%)	72.5% (62.3%, 80.3%)
Sensitivity Analysis V (participant status of VOD diagnosis by Day +30 post-HSCT was based on the EPAC assessment only, without consideration of the administration of rescue defibrotide)	66.8% (57.8%, 74.4%)	72.3% (63.0%, 79.7%)
	Number of Participants With No Event (VOD and/or Death by Day +30 post-HSCT)	
	DP	BSC
Sensitivity Analysis II (event rate is based on a composite event of either VOD or death by Day +30 post-HSCT analyzed using the CMH test stratified by risk status and age group)	140 (73.7%)	142 (78.0%)

Abbreviations: BSC = Best Supportive Care; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; DP = Defibrotide Prophylaxis; EPAC = Endpoint Adjudication Committee; HSCT = hematopoietic stem cell transplant; KM = Kaplan-Meier; mITT = Modified Intent-to-Treat; VOD = veno-occlusive disease.
Source: Tables 14.2.1.2, 14.2.1.3, 14.2.1.4, 14.2.1.5, and 14.2.1.6

Subgroup Analyses

Primary endpoint in paediatric vs adult subjects as well as in high-risk vs very high-risk subjects is summarised below.

Table 8 Subgroup Analyses of the Primary Endpoint

Subgroup	KM Estimate (95% CI) of VOD-free Survival Rate at Day +30 post-HSCT	
	DP	BSC
Pediatric	62.5% (50.2%, 72.5%)	75.0% (63.7%, 83.2%)
Adult	72.5% (58.2%, 82.6%)	69.6% (51.2%, 82.2%)
High risk	75.7% (63.9%, 84.1%)	71.3% (51.1%, 84.4%)
Very high risk	55.5% (41.5%, 67.5%)	71.3% (59.0%, 80.6%)
High risk pediatric	74.2% (60.3%, 83.9%)	78.1% (63.5%, 87.4%)
High risk adult	76.5% (51.3%, 89.8%)	53.6% (10.0%, 84.4%)
Very high risk pediatric	47.4% (28.4%, 64.2%)	69.8% (49.8%, 83.1%)
Very high risk adult	66.0% (46.5%, 79.8%)	72.6% (55.9%, 83.9%)

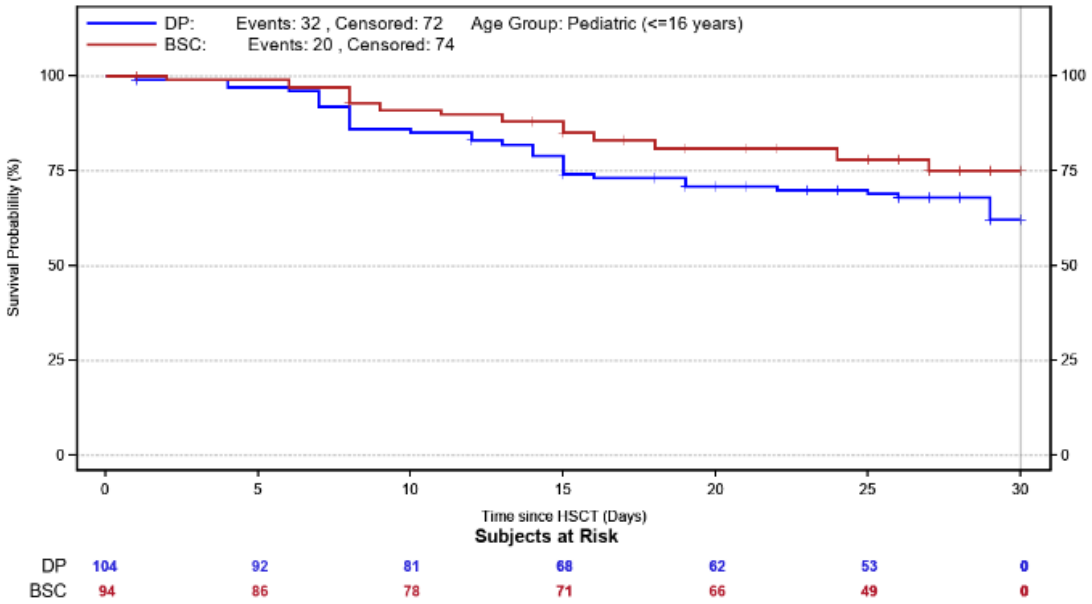
Abbreviations: BSC = Best Supportive Care; CI = confidence interval; DP = Defibrotide Prophylaxis; HSCT = hematopoietic stem cell transplant; KM = Kaplan-Meier; VOD = veno-occlusive disease.
Source: Tables 14.2.1.7, 14.2.1.8, and 14.2.1.9

Table 9. Primary Efficacy Endpoint: VOD-free Survival by Day +30 post-HSCT by Age Group ITT Analysis Set (from CSR Table 14.2.1.7) – paediatric subjects (age 16 and below)

Age Group Variable, Statistic	DP (N=190)	BSC (N=182)	DP vs. BSC
Pediatric Subjects (<=16 years)	104	94	
Number of Subjects, n(%)			
VOD/Death by Day +30 post-HSCT	32 (30.8)	20 (21.3)	
Censored	72 (69.2)	74 (78.7)	
No VOD/Death by Day +30 post-HSCT	59 (56.7)	60 (63.8)	
Other Reason	13 (12.5)	14 (14.9)	
Stage 1 Independent Unstratified Log Rank Statistic			-1.7907
Stage 2 Independent Unstratified Log Rank Statistic			-0.3187
Final Log Rank Statistic (Stage 1 and Stage 2 combined)			-1.6728
P-value			0.9528
KM Estimate of Median Time to VOD/Death in Days (95% CI)	NE	NE	
KM Estimate (%) of VOD-free Survival Rate at Day +30 post-HSCT (95% CI)	62.5 (50.2, 72.5)	75.0 (63.7, 83.2)	
Hazard Ratio(95% CI)			1.551 (0.887, 2.712)

CI = Confidence Interval; DP = Defibrotide Prophylaxis; BSC = Best Supportive Care; KM = Kaplan-Meier; VOD = Veno-Occlusive Disease
[1] Percentages were calculated with the number of subjects in each subgroup within treatment arm from the ITT Analysis Set as a denominator.
[2] P-value was calculated for the combined Stage 1 and Stage 2 log rank statistics using the method described by Cui, Hung, and Wang (1999).
[3] The hazard ratio was from a Cox proportional hazards regression model.
[4] Subgroup analyses are the same as the primary efficacy analysis, except that the hazard ratio and p-value are estimated using the asymptotic distribution of the un-stratified log rank statistic within the subgroup of interest.
Source Listing: 16.2.7.1

Figure 3. VOD -free Survival by Day +30 post-HSCT by Age Group: KM Plot with Number of Subjects at Risk ITT Analysis Set - paediatric subjects (age 16 and below)



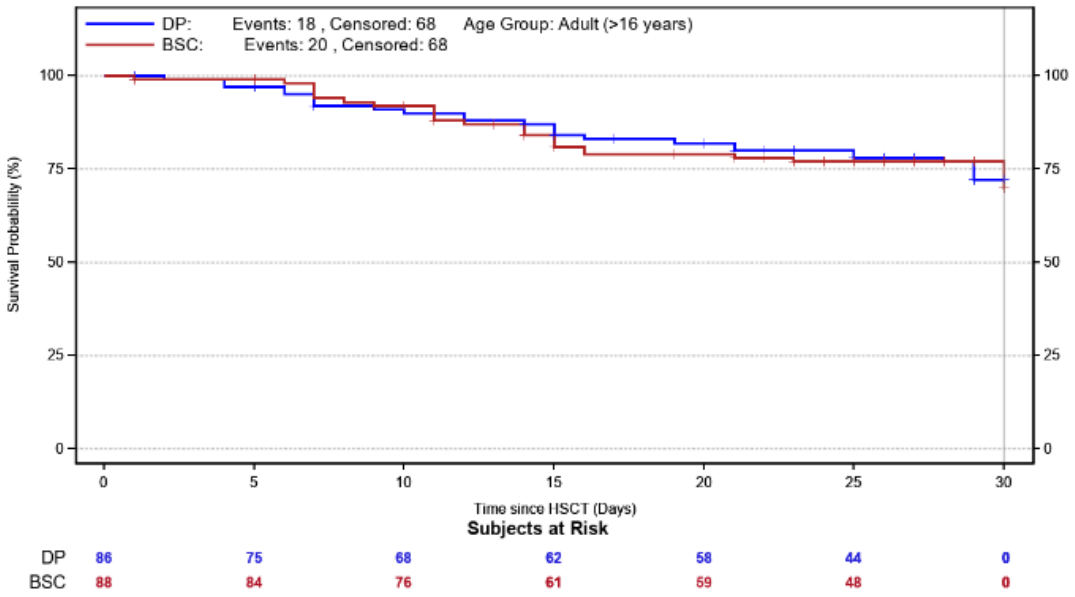
[1] VOD-free survival by Day +30 post-HSCT indicated by the vertical reference line.
Source Table: 14.2.1.7

Table 10 Primary Efficacy Endpoint: VOD-free Survival by Day +30 post-HSCT by Age Group ITT Analysis Set (CSR Table 14.2.1.7) – adult subjects (aged above 16)

Age Group Variable, Statistic	DP (N=190)	BSC (N=182)	DP vs. BSC
Adult Subjects (>16 years)	86	88	
Number of Subjects, n(%)			
VOD/Death by Day +30 post-HSCT	18 (20.9)	20 (22.7)	
Censored	68 (79.1)	68 (77.3)	
No VOD/Death by Day +30 post-HSCT	53 (61.6)	53 (60.2)	
Other Reason	15 (17.4)	15 (17.0)	
Stage 1 Independent Unstratified Log Rank Statistic			-0.8971
Stage 2 Independent Unstratified Log Rank Statistic			1.7700
Final Log Rank Statistic (Stage 1 and Stage 2 combined)			0.2189
P-value			0.4134
KM Estimate of Median Time to VOD/Death in Days (95% CI)	NE	NE	
KM Estimate (%) of VOD-free Survival Rate at Day +30 post-HSCT (95% CI)	72.5 (58.2, 82.6)	69.6 (51.2, 82.2)	
Hazard Ratio(95% CI)			0.972 (0.514, 1.839)

CI = Confidence Interval; DP = Defibrotide Prophylaxis; BSC = Best Supportive Care; KM = Kaplan-Meier; VOD = Veno-Occlusive Disease
[1] Percentages were calculated with the number of subjects in each subgroup within treatment arm from the ITT Analysis Set as a denominator.
[2] P-value was calculated for the combined Stage 1 and Stage 2 log rank statistics using the method described by Cui, Hung, and Wang (1999).
[3] The hazard ratio was from a Cox proportional hazards regression model.
[4] Subgroup analyses are the same as the primary efficacy analysis, except that the hazard ratio and p-value are estimated using the asymptotic distribution of the un-stratified log rank statistic within the subgroup of interest.
Source Listing: 16.2.7.1

Figure 4 VOD -free Survival by Day +30 post-HSCT by Age Group: KM Plot with Number of Subjects at Risk ITT Analysis Set - adult subjects (aged above 16)



[1] VOD-free survival by Day +30 post-HSCT indicated by the vertical reference line.
Source Table: 14.2.1.7

An additional subgroup analysis was to be performed by prior liver disease status; however, all participants in the ITT Analysis Set had prior liver disease.

Concordance between EPAC- and Investigator-assessed VOD-free Survival

Concordance between EPAC- and investigator-assessed VOD by Day +30 post-HSCT was analysed for each of the 2 treatment arms and overall. A total of 35 participants (9.9%) were assessed to have VOD by Day +30 post-HSCT by both the EPAC and investigator, and a total of 221 participants (62.6%) were assessed to not have VOD by Day +30 post-HSCT by both the EPAC and investigator. Overall, EPAC and investigator assessments were concordant in 256 (72.5%) cases. Out of the 35 cases where the EPAC and the investigator both diagnosed VOD, the VOD diagnosis dates were concordant in 12 (34.3%) cases. In a total of 50 participants (14.2%), the EPAC assessed the participant as having VOD while the investigator assessed the participant as not having VOD. Concordance was similar between the 2 treatment arms. Of note, the EPAC could assess VOD as 'Not evaluable', whereas the investigator could not (ie, 'Yes' and 'No' were the only options). The EPAC assessed 13 participants (3.7%) overall as not evaluable. The investigator-assessed VOD-free survival rates at Day +30 post-HSCT were similar between the DP and BSC treatment arms, with KM estimates (95% CIs) of 85.0% (78.6%, 89.7%) and 80.4% (73.4%, 85.8%), respectively.

Table 11. Concordance between PI and EPAC Assessed VOD by Day +30 Post-HSCT mITT analysis Set (from CSR Table 14.2.1.11)

	DP (N=179)	BSC (N=174)	Total (N=353)
Investigator VOD/EPAC Assessed VOD			
Yes/Yes	18 (10.1)	17 (9.8)	35 (9.9)
Yes/No	3 (1.7)	1 (0.6)	4 (1.1)
No/Yes	29 (16.2)	21 (12.1)	50 (14.2)
No/No	109 (60.9)	112 (64.4)	221 (62.6)
Yes/Not evaluable	1 (0.6)	0	1 (0.3)
No/Not evaluable	8 (4.5)	4 (2.3)	12 (3.4)
Investigator VOD/EPAC Assessed VOD = Yes/Yes			
n	18	17	35
VOD Diagnosis Dates Match	6 (33.3)	6 (35.3)	12 (34.3)
VOD Diagnosis Dates Do Not Match	12 (66.7)	11 (64.7)	23 (65.7)

DP = Defibrotide Prophylaxis; BSC = Best Supportive Care; EPAC = Endpoint Adjudication Committee; VOD = Veno-Occlusive Disease
[1] Percentages for Investigator/EPAC agreement were calculated using number of subjects in each arm from the mITT Analysis Set as a denominator.
[2] Percentages for matching diagnosis dates were calculated using total number of Yes/Yes agreements in each arm as a denominator.
Source Listing: 16.2.7.1 and 16.2.7.3

Assessor's comment:

The primary efficacy endpoint was not met; there was no preventive effect of defibrotide on VOD-free survival day 30+ post-HSCT in the defibrotide group as compared to best supportive care. There was a numerical imbalance in favour of best supportive care; this was particularly pronounced in the paediatric population. In the overall ITT population, VOD/death occurred in 50/190 subjects in the defibrotide arm (26.3%) and 40/182 subjects in the BSC arm (22%). The KM VOD-free survival estimates (95% CIs) at Day +30 post-HSCT in the defibrotide arm vs the BSC arm were 66.8% (57.8%, 74.4%) and 72.5% (62.3%, 80.4%), respectively. In the paediatric population, VOD/death occurred in 32/104 subjects in the defibrotide arm (30.8%) and 20/94 subjects in the BSC arm (21.3%). The KM VOD-free survival estimates (95% CIs) at Day +30 post-HSCT in the paediatric defibrotide arm vs the BSC arm were (95% CIs) 62.5% (50.2%, 72.5%) and 75.0% (63.7%, 83.2%), respectively.

There is no clear presentation of the number of VOD and the number of deaths that contributed to the primary efficacy endpoint events. It is stated below that there were in total 20 participants (10 in each treatment arm) who died during the prophylaxis phase of the study (see Safety below); in a different analysis there were a total of 15 deaths up to day +30 post-HSCT (10 in the defibrotide arm and 5 in the BSC arm, all but one in the defibrotide group with an adverse event as the primary cause of death, see also Safety). There were 85 adjudicated VOD events, and thus at least 15 deaths up to Day +30 post-HSCT. Subjects who were diagnosed with VOD were to be treated with defibrotide as rescue therapy and would then be censored from the prophylaxis analyses. Given that there were in total 90 primary efficacy outcome events, the figures appear not to match. The MAH should clarify the number of events of VOD and deaths respectively that contributed to the primary efficacy endpoint, and whether the presented data on primary efficacy outcome events includes any subjects with more than one event (**LoQ**).

The terminology used by the MAH is slightly inconsistent in the sense that data is labelled as "censored" in the context of VOD-free survival analysis and as "missing" in other contexts. While the terms are similar, the difference is that "missing" data is completely unknown and "censored" data partially unknown, i e for subjects censored at 30 days follow-up, it is known that the event did not happen before 30 days FU, which is more information compared to have no information at all (ie no event). This difference is relevant here because the results (primary efficacy endpoint – ITT analysis set, Table 6 above) show statistical test results from a log rank test comparing VOD-free survival times

across the total follow-up time and the VOD-free survival rate by +30 post-HSCT as landmark time. While the log rank test uses all VOD-free survival times across the follow-up time, the VOD-free survival rate at landmark time by +30 post-HSCT uses a single timepoint for comparison. Therefore, the VOD-free survival rate at landmark time is not a completely consistent representation of the descriptive treatment effect on VOD-free survival times tested by the log rank test because the "estimand" is somewhat different between the survival rate analysis (ie difference in distribution of events) vs survival time analysis (ie difference in distribution of survival times). While it would be appropriate for a survival rate analysis to label patients with "has event" vs "has no event" vs "missing", for a survival time analysis the patients should be labelled as "has event" vs "censored" would be appropriate. Censored data can be caused by end of follow-up without previous event or other intercurrent events which make the data not observable (eg study discontinuation). Given the large proportion of 'other reason' for censoring in the presentation of primary efficacy outcome events, the MAH is asked to present these other reasons in more detail, including any imbalance between treatment groups (**LoQ**).

For the paediatric population (aged 16 and below), the difference between the VOD-free survival rate at landmark time +30 post-HSCT (69.2% in DP, 78.7 % in BSC, RR=1.45) and from the KM curve (62.5% in DP vs. 75%, RR=1.5) are similar but not identical, because the KM curve uses an estimation method adjusting for the patients no longer at risk of having an event at +30 post-HSCT, ie an adjustment for censored data. Overall, the effect sizes for Relative Risk (RR) from VOD-free survival rate =1.45, from KM with RR = 1.5 and from the Hazard Ratio from Cox PH =1.55 are reasonably consistent (attributing differences to differences in methods).

The primary analysis and sensitivity analyses (except worst case analysis) show numerically increased, statistically non-significant risks for the DP group of around HR= 1.27. The worst-case (implausible) scenario gives a nominally statistically hazard ratio of HR =1.977 [CI95% 1.349, 2.897]. For the worst-case scenario, the MAH has used a "worst-case" imputation, which is also described in the "Statistical Analysis Plan" document (4.2.10, primary, 4.5.3.1 sensitivity analysis), where all censored patients imputed as having an event in the DP arm, but as no event (censored) in the BSC (control) arm. This assumption is not plausible, but a conservative assumption to estimate a lower boundary of the effect size.

There was a clear discordance between the endpoint adjudication committee (EPAC) assessment and investigators' assessment of VOD. The majority of cases adjudicated as VOD were not assessed as VOD by investigators. It is understood from the tables above that there were in total 85 adjudicated cases of VOD in the mITT population (all subjects in the ITT population who underwent HSCT), 47/179 in the defibrotide group and 38/174 in the BSC group. Of those, 50/85 were not assessed as VOD by investigators but were adjudicated by the EPAC; 4 cases were assessed as VOD by investigators but not by the EPAC. There was an imbalance between treatment arms in assessment of VOD, with more cases assessed as VOD by the EPAC only in the defibrotide group as compared to the BSC group. In addition to the overall discordance between the blinded EPAC and the non-blinded investigators, in the 35 cases assessed as VOD by both investigators and EPAC, the date of VOD diagnosis did not match in two thirds of the cases. These data are interpreted in that there was a low recognition of VOD among investigators, especially in the open-label defibrotide treatment group. This is of particular interest given that this study had a blinded EPAC assessing all patients in the study, which has not been the case in previous defibrotide trials.

As stated in the description of participant flow above, there were 56 subjects who developed VOD during the prophylaxis phase and received defibrotide as rescue treatment. The decision to start rescue treatment was based on the investigator's assessment of VOD. However, it appears that there were in total 40 cases of VOD recognised by investigators. The MAH is asked to explain this

discrepancy and to discuss the vast difference between investigators and EPAC assessments of VOD and date of VOD diagnosis in more detail, including the diagnostic criteria used and their clinical relevance (**LoQ**).

The exact type of best supportive care used has not been presented. Since there was no prespecified BSC, it is unclear if there is any imbalance between treatment arms. Although there is no approved product for prophylaxis of VOD, a Cochrane review on prophylaxis of VOD from 2015 concluded that there was low or very low quality evidence that ursodeoxycholic acid may reduce the incidence of hepatic VOD, all-cause mortality and mortality due to VOD in HSCT recipients. However, the optimal regimen is not well-defined. The Cochrane review also concluded that there is insufficient evidence to support the use of heparin, LMWH, defibrotide, glutamine, FFP, antithrombin III, and PGE1, and that further high-quality RCTs are needed. From the presentation of concomitant therapy (see Safety below), the majority of study subjects were treated with ursodeoxycholic acid (310/372 or 83.3%) with a similar proportion in each treatment group; the assessment of concomitant therapy is however hampered by the non-consistent capture of concomitant therapy during the study (see below).

Overall, these data show that defibrotide had no effect as compared to best supportive care for prophylaxis of VOD. This lack of efficacy does not translate into questioning efficacy for the approved treatment indication (the data on outcome of defibrotide treatment as rescue treatment for those who developed VOD are however of interest for the approved indication, see secondary endpoints below). However, there was a numerical imbalance in favour of best supportive care; this was particularly pronounced in the paediatric population, which is considered worrisome from a safety perspective. This trend of worse outcome in the defibrotide group is found of importance also for the approved indication, given the similarities in the populations studied. Also, these data should be seen in light of previous data on prophylaxis submitted within the MAA in 2013, in which the death rate was higher in the prevention study when children who did not develop VOD and received DF were compared with subjects in the control arm who did not develop VOD. The MAH is asked to discuss these findings in relation to the totality of data for the approved indications for Defitelio (**LoQ**).

Secondary efficacy endpoints

Because the primary efficacy endpoint was not met, hypothesis testing was not performed for the key secondary efficacy endpoint and that analysis is descriptive only. The analyses of other secondary efficacy endpoints were descriptive; nominal p-values are reported.

The VOD-free survival rates at Day +100 post-HSCT as adjudicated by the independent EPAC (key secondary endpoint) were, with KM VOD-free survival estimates (95% CIs), 49.8% (26.1%, 69.5%) in the defibrotide arm and 57.1% (36.6%, 73.1%) in the BSC arm. The HR of the DP arm with respect to the BSC arm is 1.208, with a 95% CI of 0.835 to 1.748.

A total of 47 participants (24.7%) in the DP arm and 38 participants (20.9%) in the BSC arm experienced EPAC-assessed VOD by Day +30 post-HSCT. The proportion of participants who experienced VOD after Day +30 post-HSCT and on or before Day +100 post-HSCT was similar in the 2 treatment arms (6 participants [3.2%] in the DP arm, and 5 participants [2.7%] in the BSC arm). The proportion of participants who experienced VOD after Day +30 post-HSCT and on or before Day +180 post-HSCT, was also similar in the 2 treatment arms (6 participants [3.2%] in the DP arm, and 5 participants [2.7%] in the BSC arm). The diagnosis of VOD through Day +100 post-HSCT was made by the EPAC, and the diagnosis of VOD after Day +100 post-HSCT was based on investigator assessments.

The VOD-free survival rates at Day +180 post-HSCT were similar between the DP and BSC treatment arms, with KM VOD-free survival estimates (95% CIs) of 34.6% (18.2%, 51.8%) and 42.8% (26.7%, 58.0%), respectively.

Of the participants with malignant primary disease history, 22 of 147 participants (15.0%) in the DP arm and 11 of 139 participants (7.9%) in the BSC arm experienced NRM (Non-relapse mortality) by Day +100 post-HSCT; 25 of 147 participants (17.0%) in the DP arm and 16 of 139 participants (11.5%) in the BSC arm experienced NRM by Day +180 post-HSCT. The HR (95% CI) of the DP arm with respect to the BSC arm is 2.243 (1.082, 4.647) at Day +100 post-HSCT and 1.885 (0.989, 3.592) at Day +180 post-HSCT.

At Day +30 post-HSCT, 8 participants (4.2%) in the DP arm and 8 participants (4.4%) in the BSC arm had VOD-associated MOD. At both Day +100 post-HSCT and Day +180 post-HSCT, 9 participants (4.7%) in the DP arm and 10 participants (5.5%) in the BSC arm had VOD-associated MOD.

Of the participants diagnosed by the investigator with VOD by Day +30 post-HSCT, 6 of 23 participants (26.1%) in the DP arm and 15 of 29 participants (51.7%) in the BSC arm experienced VOD resolution by Day +180 post-HSCT. The HR of the DP arm with respect to the BSC arm is 0.316, with a 95% CI of 0.112 to 0.893.

Assessor's comment:

Since the primary efficacy endpoint was not met, the data on secondary efficacy endpoints are descriptive only. There are some worrying results regarding the key secondary efficacy endpoint with a numerical difference between treatment arms (VOD-free survival at Day +100 post HSCT of 49.8% in the defibrotide arm as compared to 57.1% in the best supportive care arm); even though the 95% CIs overlap and this is descriptive data only, there is thus a similar trend of worse outcome in the defibrotide group as for the primary efficacy outcome.

What is further worrisome is the non-relapse mortality; again, since these are descriptive data, some caution is warranted. However, 22 of 147 participants (15.0%) in the DP arm and 11 of 139 participants (7.9%) in the BSC arm experienced NRM by Day +100 post-HSCT. Of the participants with malignant primary disease history, 25 of 147 participants (17.0%) in the DP arm and 16 of 139 participants (11.5%) in the BSC arm experienced NRM by Day +180 post-HSCT.

The data on participants diagnosed with VOD by Day 30 post-HSCT show resolution of VOD by day 180 post-HSCT in 6/23 or 26.1% of subjects in the defibrotide arm and 15/29 or 51.7% of subjects in the best supportive care arm. The severity of the diagnosed VOD is not clear, thus it should be clarified if defibrotide was given in accordance with the Defitelio label (indicated in severe VOD only) or not (**LoQ**); however, the difference between treatment arms are considered to clearly disfavour those who had been treated with defibrotide for prophylaxis. The resolution rates appear to be in line with, or slightly lower than, what is described in literature for spontaneous resolution of VOD. It is assumed that all subjects who developed VOD as judged by investigator were treated with defibrotide regardless of treatment allocation for the prophylaxis phase; the MAH is asked to verify this assumption. Also, since a large proportion of cases of VOD were defined by the EPAC (and assumed not to have been treated for VOD by investigators) the MAH should present the outcome in terms of resolution of VOD in those treated with defibrotide for rescue as compared to those who developed VOD but were not treated with defibrotide, both for the entire study population and divided by age group (paediatric subjects vs adults) (**LoQ**).

For the additional secondary endpoints of health-related QoL; incidence of grades 2, 3 and 4 acute GvHD and incidence of chronic GvHD by Day 180 +HSCT; graft failure and time to neutrophil and platelet engraftment, these and the exploratory endpoints are discussed in the Safety section below.

Overall, in line with the primary efficacy endpoint, descriptive data on the secondary efficacy endpoints indicate at best no effect of defibrotide but a possible unfavourable effect on VOD-free survival, non-relapse mortality and resolution of VOD.

6.4. Discussion

Design and conduct of clinical studies

Study 15-007 was a randomised open-label study aimed at assessing the prophylactic effect of adding defibrotide to standard of care (best supportive care) to prevent VOD in children (>1 month) and adults who were scheduled to undergo HSCT. The study included only subjects in whom the risk of developing VOD was expected to be high or very high, based on what is currently known about the disease, mainly based on the planned conditioning regimens. Haemodynamically unstable patients and patients with acute bleeding or recent treatment that increases the risk of bleeding were excluded. Thus, the population studied is considered suitable for assessing any prophylactic effect of defibrotide based on the assumed (very) high risk of VOD while the risk of bleeding (which is a labelled adverse reaction of defibrotide) would be low. The study aimed at prevention of VOD, which is not an approved

indication for Defitelio. However, subjects included who developed VOD would receive defibrotide as rescue treatment, which is according to the label albeit for **severe** VOD only.

The study was stopped based on futility after evaluation of the pre-planned interim analysis including data from 280 subjects. In total, there were 372 randomised subjects: 190 allocated to defibrotide in addition to best supportive care (BSC), 182 allocated to (BSC) only.

The defibrotide dose used in the defibrotide arm (on top of best supportive care) of 25 mg/kg/day divided into 4 equal doses is the same as the approved posology for Defitelio for treatment of severe VOD, which is to be administered for a minimum of 21 days and continued until the symptoms and signs of severe VOD resolve. Thus, the exposure to defibrotide for VOD prophylaxis in this study was similar to the label for treatment of severe VOD, and the approved posology was also used for rescue treatment of VOD. Standard of care therapy was based on local institutional guidelines and patient need as judged by investigators; there was no formal recommendation on best supportive care.

The primary objective was to compare the efficacy of defibrotide prophylaxis in addition to BSC vs BSC alone for the prevention of VOD, with the primary endpoint VOD-free survival rate by Day +30 post-HSCT. An independent endpoint adjudication committee that was blinded to study treatment assignment determined whether criteria for the primary and key secondary efficacy endpoints were met, using modified Seattle criteria for diagnosis of VOD. This is considered a strength of the study; a similar blinded independent EPAC was not used in previous defibrotide studies. This is further of interest given the large discrepancy between VOD as adjudicated by investigators vs by the EPAC (see Efficacy data below).

Mortality was included in the primary efficacy endpoint (VOD-free survival rate by Day +30) and the secondary endpoints VOD-free survival by Day +100 and +180 post-HSCT, and NRM (non-relapse mortality) by day 100 and 180 post-HSCT. There is also a post-hoc analysis on overall mortality, see Safety below.

For the entire study population, demographics and baseline characteristics were similar in the two treatment arms. The most frequent underlying disease was acute lymphoblastic leukaemia (100 participants [26.9%]), acute myelogenous leukaemia (96 participants [25.8%]), and neuroblastoma (57 participants [15.3%]). Transplant data for the 353/372 subjects who underwent HSCT have been provided; the majority of these had allogenic grafts. Myeloablative conditioning was given to approximately two thirds of subjects.

There were 198 paediatric subjects in the study, thus constituting more than half of the study population, with a median age of 4.5 yrs (range 0-16 yrs) at screening; 104 in the defibrotide group and 94 in the SoC group. Neuroblastoma was the most common primary disease followed by ALL and AML in the paediatric group. For 59/198 children, the primary disease was recurrent at baseline.

One third of the ITT population had major protocol deviations, primarily related to study procedures/assessments (not further specified) and informed consent form processing/timing. The MAH should provide the most frequent reasons for deviation in study procedures/assessments and discuss the overall integrity of the study given the large number of major protocol deviations (**LoQ**).

Efficacy data and additional analyses

The primary efficacy endpoint was not met; there was no preventive effect of defibrotide on VOD-free survival day 30+ post-HSCT in the defibrotide group as compared to best supportive care. There was a numerical imbalance in favour of best supportive care; this was particularly pronounced in the paediatric population. In the overall ITT population, VOD/death occurred in 50/190 subjects in the

defibrotide arm (26.3%) and 40/182 subjects in the BSC arm (22%). The VOD-free survival rates at Day +30 post-HSCT in the defibrotide arm vs the BSC arm with KM VOD-free survival estimates (95% CIs) of 66.8% (57.8%, 74.4%) and 72.5% (62.3%, 80.4%), respectively. In the paediatric population, VOD/death occurred in 32/104 subjects in the defibrotide arm (30.8%) and 20/94 subjects in the BSC arm (21.3%). The VOD-free survival rates at Day +30 post-HSCT in the paediatric defibrotide arm vs the BSC arm with KM VOD-free survival estimates (95% CIs) of 62.5% (50.2%, 72.5%) and 75.0% (63.7%, 83.2%), respectively.

There is no clear presentation of the number of VOD and the number of deaths that contributed to the primary efficacy endpoint events. It is stated below that there were in total 20 participants (10 in each treatment arm) who died during the prophylaxis phase of the study (see Safety below); in a different analysis there were a total of 15 deaths up to day +30 post-HSCT (10 in the defibrotide arm and 5 in the BSC arm, all but one in the defibrotide group with an adverse event as the primary cause of death, see also Safety). There were 85 adjudicated VOD events, and thus at least 15 deaths up to Day +30 post-HSCT. Subjects who were diagnosed with VOD were to be treated with defibrotide as rescue therapy and would then be censored from the prophylaxis analyses. Given that there were in total 90 primary efficacy outcome events, the figures appear not to match. The MAH should clarify the number of events of VOD and deaths respectively that contributed to the primary efficacy endpoint (**LoQ**).

The terminology used by the MAH is slightly inconsistent in the sense that data is labelled as "censored" in the context of VOD-free survival analysis and as "missing" in other contexts. While the terms are similar, the difference is that "missing" data is completely unknown and "censored" data partially unknown, i e for subjects censored at 30 days follow-up, it is known that the event did not happen before 30 days FU, which is more information compared to have no information at all (ie no event). This difference is relevant here because the results (primary efficacy endpoint – ITT analysis set, Table 6 above) show statistical test results from a log rank test comparing VOD-free survival times across the total follow-up time and the VOD-free survival rate by +30 post-HSCT as landmark time. While the logrank test uses all VOD-free survival times across the follow-up time, the VOD-free survival rate at landmark time by +30 post-HSCT uses a single timepoint for comparison. Therefore, the VOD-free survival rate at landmark time is not a completely consistent representation of the descriptive treatment effect on VOD-free survival times tested by the logrank test because the "estimand" is somewhat different between the survival rate analysis (ie difference in distribution of events) vs survival time analysis (ie difference in distribution of survival times). While it would be appropriate for a survival rate analysis to label patients with " has event" vs " has no event" vs "missing", for a survival time analysis the patients should be labelled as "has event" vs "censored" would be appropriate. Censored data can be caused by end of follow-up without previous event or other intercurrent events which make the data not observable (eg study discontinuation). Given the large proportion of 'other reason' for censoring in the presentation of primary efficacy outcome events, the MAH is asked to present these other reasons in more detail, including any imbalance between treatment groups (**LoQ**).

For the paediatric population (aged 16 and below), the difference between the VOD-free survival rate at landmark time +30 post-HSCT (69.2% in DP, 78.7 % in BSC, RR=1.45) and from the KM curve (62.5% in DP vs. 75%, RR=1.5) are similar but not identical, because the KM curve uses an estimation method adjusting for the patients no longer at risk of having an event at +30 post-HSCT, ie an adjustment for censored data. Overall, the effect sizes for Relative Risk (RR) from VOD-free survival rate =1.45, from KM with RR = 1.5 and from the Hazard Ratio from Cox PH =1.55 are reasonably consistent (attributing differences to differences in methods).

The primary analysis and sensitivity analyses (except worst case analysis) show numerically increased, statistically non-significant risks for the DP group of around HR= 1.27. The worst-case (implausible)

scenario gives a nominally statistically hazard ratio of HR =1.977 [CI95% 1.349, 2.897]. For the worst-case scenario, the MAH has used a "worst-case" imputation, which is also described in the "Statistical Analysis Plan" document (4.2.10, primary, 4.5.3.1 sensitivity analysis), where all censored patients imputed as having an event in the DP arm, but as no event (censored) in the BSC (control) arm. This assumption is not plausible, but a conservative assumption to estimate a lower boundary of the effect size.

There was a clear discordance between the endpoint adjudication committee (EPAC) assessment and investigators' assessment of VOD. Most cases adjudicated as VOD were not assessed as VOD by investigators. It is understood from the tables above that there were in total 85 adjudicated cases of VOD in the mITT population (all subjects in the ITT population who underwent HSCT), 47/179 in the defibrotide group and 38/174 in the BSC group. Of those, 50/85 were not assessed as VOD by investigators but were adjudicated by the EPAC; 4 cases were assessed as VOD by investigators but not by the EPAC. There was an imbalance between treatment arms in assessment of VOD, with more cases assessed as VOD by the EPAC only in the defibrotide group as compared to the BSC group. In addition to the overall discordance between the blinded EPAC and the non-blinded investigators, in the 35 cases assessed as VOD by both investigators and EPAC, the date of VOD diagnosis did not match in two thirds of the cases. These data are interpreted in that there was a low recognition of VOD among investigators, especially in the open-label defibrotide treatment group. This is of particular interest given that this study had a blinded EPAC assessing all patients in the study, which has not been the case in previous defibrotide trials.

As stated in the description of participant flow above, there were 56 subjects who developed VOD during the prophylaxis phase and received defibrotide as rescue treatment. The decision to start rescue treatment was based on the investigator's assessment of VOD. However, it appears that there were in total 40 cases of VOD recognised by investigators. The MAH is asked to explain this discrepancy and to discuss the vast difference between investigators and EPAC assessments of VOD and date of VOD diagnosis in more detail, including the diagnostic criteria used and their clinical relevance (**LoQ**).

The exact type of best supportive care used has not been presented. Since there was no prespecified BSC, it is unclear if there is any imbalance between treatment arms. Although there is no approved product for prophylaxis of VOD, a Cochrane review on prophylaxis of VOD from 2015 concluded that there was low or very low quality evidence that ursodeoxycholic acid may reduce the incidence of hepatic VOD, all-cause mortality and mortality due to VOD in HSCT recipients. However, the optimal regimen is not well-defined. The Cochrane review also concluded that there is insufficient evidence to support the use of heparin, LMWH, defibrotide, glutamine, FFP, antithrombin III, and PGE1, and that further high-quality RCTs are needed. From the presentation of concomitant therapy (see Safety below), the majority of study subjects were treated with ursodeoxycholic acid (310/372 or 83.3%) with a similar proportion in each treatment group; the assessment of concomitant therapy is however hampered by the non-consistent capture of concomitant therapy during the study (see below).

Overall, these data show that defibrotide had no effect as compared to best supportive care for prophylaxis of VOD. This lack of efficacy does not translate into questioning efficacy for the approved treatment indication (the data on outcome of defibrotide treatment as rescue treatment for those who developed VOD are however of interest for the approved indication, see secondary endpoints below). The numerical imbalance in favour of best supportive care for VOD-free survival both during the prophylaxis period of study 15-007 and more pronounced during the rescue treatment period are of concern, primarily from a safety perspective. The population studied is similar to the population covered by the approved indication, and these data should be seen in light of previous data on prophylaxis submitted within the MAA in 2013, in which the death rate was higher in the prevention

study when children who did not develop VOD and received DF were compared with subjects in the control arm who did not develop VOD. The MAH should discuss the apparent imbalance in mortality with defibrotide treatment, in relation to the approved indication (**LoQ, safety MO**).

Since the primary efficacy endpoint was not met, the data on secondary efficacy endpoints are descriptive only. There are some worrying results regarding the key secondary efficacy endpoint with a numerical difference between treatment arms (VOD-free survival at Day +100 post HSCT of 49.8% in the defibrotide arm as compared to 57.1% in the best supportive care arm); even though the 95% CIs overlap and this is descriptive data only, there is thus a similar trend of worse outcome in the defibrotide group as for the primary efficacy outcome.

What is further worrisome is the non-relapse mortality; again, since these are descriptive data, some caution is warranted. However, 22 of 147 participants (15.0%) in the DP arm and 11 of 139 participants (7.9%) in the BSC arm experienced NRM by Day +100 post-HSCT. Of the participants with malignant primary disease history, 25 of 147 participants (17.0%) in the DP arm and 16 of 139 participants (11.5%) in the BSC arm experienced NRM by Day +180 post-HSCT.

The data on participants diagnosed with VOD by Day 30 post-HSCT show resolution of VOD by day 180 post-HSCT in 6/23 or 26.1% of subjects in the defibrotide arm and 15/29 or 51.7% of subjects in the best supportive care arm. The severity of the diagnosed VOD is not clear, thus it should be clarified if defibrotide was given in accordance with the Defitelio label (indicated in severe VOD only) or not (**LoQ**); however, the difference between treatment arms are considered to clearly disfavour those who had been treated with defibrotide for prophylaxis. The resolution rates appear to be in line with, or slightly lower than, what is described in literature for spontaneous resolution of VOD. It is assumed that all subjects who developed VOD as judged by investigator were treated with defibrotide regardless of treatment allocation for the prophylaxis phase; the MAH is asked to verify this assumption (**LoQ**). Also, since a large proportion of cases of VOD were defined by the EPAC (and assumed not to have been treated for VOD by investigators) the MAH should present the outcome in terms of resolution of VOD in those treated with defibrotide for rescue as compared to those who developed VOD but were not treated with defibrotide, both for the entire study population and divided by age group (paediatric subjects vs adults) (**LoQ**).

For the additional secondary endpoints of health-related QoL; incidence of grades 2, 3 and 4 acute GvHD and incidence of chronic GvHD by Day 180 +HSCT; graft failure and time to neutrophil and platelet engraftment, these and the exploratory endpoints are discussed in the Safety section below.

Overall, in line with the primary efficacy endpoint, descriptive data on the secondary efficacy endpoints indicate at best no effect of defibrotide but a possible unfavourable effect on VOD-free survival, non-relapse mortality and resolution of VOD.

Rapporteur's conclusion on efficacy

Study 15-007 was a randomised open-label study aimed at assessing the prophylactic effect of adding defibrotide to standard of care in a population with assumed (very) high risk of VOD while the risk of bleeding would be low. Prevention of VOD is not an approved indication for Defitelio. However, subjects included who developed VOD would receive defibrotide as rescue treatment, which is according to the label albeit for severe VOD only.

The study was stopped after an interim analysis based on futility; 372 subjects were randomised which was nevertheless in line with the originally anticipated study size.

The primary efficacy endpoint (VOD-free survival rate by Day +30 post-HSCT) was not met; there was no preventive effect of defibrotide on VOD-free survival day 30+ post-HSCT in the defibrotide group as compared to best supportive care. There was a numerical imbalance in favour of best supportive care;

this was particularly pronounced in the paediatric population. This is of concern, primarily from a safety perspective. The population studied is similar to the population covered by the approved indication, and these data should be seen in light of previous data on prophylaxis submitted within the MAA in 2013, in which the death rate was higher in the prevention study when children who did not develop VOD and received DF were compared with subjects in the control arm who did not develop VOD. The MAH should discuss the apparent imbalance in mortality with defibrotide treatment (**LoQ, safety MO**).

One strength of study 15-007 was the independent blinded assessment of the primary efficacy endpoint, which has not been done in previous defibrotide studies and demonstrating a large discrepancy between blinded, independent assessment of VOD and investigator's assessment of VOD. Further clarifications are warranted regarding assessment of VOD, severity of VOD and outcome on VOD resolution in subjects treated with defibrotide as compared to those not treated with defibrotide.

7. Clinical Safety aspects

7.1. Methods – analysis of data submitted

Safety data collection in study 15-007

For the safety analyses, 2 study phases were defined with respect to the administration of rescue defibrotide:

•Prophylaxis Phase – For the overall safety population, this phase was defined as the period between baseline and start date of rescue defibrotide, if applicable, or the period between baseline and Day +180 post-HSCT if no VOD occurred. (End date of Prophylaxis Phase = start date of rescue defibrotide – 1 or Day +180 post-HSCT if no VOD occurred)

•Treatment Phase – For the subset of patients in the safety population who developed VOD and received rescue defibrotide, this phase is defined as the period between start date of rescue defibrotide and Day +180 post-HSCT. (Start date of Treatment Phase = start date of rescue defibrotide)

A TEAE was defined as any event with onset date on or after the first dose of study treatment (either DP or conditioning regimen) or any ongoing event that worsened in severity after the date of the first dose of study treatment through the protocol-specific reporting period. Only TEAEs with the onset date on or before the end of the protocol-specific AE reporting period were included in summary tables unless otherwise specified. For all AE summaries, if a patient has more than 1 AE within a preferred term, the patient is counted only once at the maximum severity and with the closest relationship to study drug. If a patient has more than 1 AE within a system organ class, the patient is similarly counted once when reporting results for that system organ class.

7.2. Results

Patient exposure

The Safety Analysis Set included 181 subjects randomised to the defibrotide arm who received at least 1 dose of defibrotide and 174 subjects randomised to the best supportive care arm who received at least 1 dose of study drug (defibrotide or conditioning regimen).

The median (min, max) duration of treatment for participants in the DP arm during the prophylaxis phase of the study was 29.0 (1, 43) days (Table 6). The median (min, max) number of doses received was 111.0 (1, 172) doses and the median daily dose was 24.03 (0.0, 27.5) mg/kg/day. The median (min, max) duration of treatment during the rescue phase was 16.0 (1, 78) days in the DP arm and 22.0 (1, 49) days in the BSC arm. The median (min, max) number of doses received was 61.0 (2, 284) and 82.0 (2, 192) in the DP and BSC, respectively, and the median daily dose was 23.06 (0.0, 26.5) and 23.23 (0.0, 25.9) mg/kg/day, respectively.

Prior and Concomitant Therapy

Use of relevant prior medications were reported for most participants (333 of 372 participants [89.5%]; Table 14.1.7.1). The most frequently reported relevant prior medications overall were ursodeoxycholic acid (169 participants [45.4%]), Bactrim (125 participants [33.6%]), aciclovir (119 participants [32.0%]), paracetamol (81 participants [21.8%]), and fluconazole (78 participants [21.0%]).

Relevant concomitant medications reported in at least 50% of participants overall include aciclovir (319 participants [85.8%]), ursodeoxycholic acid (310 participants [83.3%]), paracetamol (307 participants [82.5%]), furosemide (294 participants [79.0%]), ondansetron (238 participants [64.0%]), Bactrim (236 participants [63.4%]), magnesium sulfate (206 participants [55.4%]), filgrastim (201 participants [54.0%]), fluconazole (191 participants [51.3%]), and potassium chloride (186 participants [50.0%]).

Due to an error in the original protocol and early versions of the ICFs, concomitant medications were not captured consistently in the clinical database. Per the EPAC, this inconsistent reporting did not impact their assessment of VOD, and concomitant medications were consistently captured in the pharmacovigilance database for reportable events described in the individual participant narratives (Section 11). The majority of participants received a conditioning regimen (354 of 372 participants [95.2%] overall). The most common conditioning regimens overall included fludarabine (186 participants [50.0%]), busulfan (173 participants [46.5%]), cyclophosphamide (131 participants [35.2%]), antithymocyte immunoglobulin (127 participants [34.1%]), and melphalan (113 participants [30.4%]). The conditioning regimens for HSCT were generally similar across treatment arms. One participant received a conditioning regimen but did not undergo HSCT (Listings 16.2.1.1 and 16.2.6.3) and is not included in the mITT Analysis Set (Section 4.3).

Assessor's comment:

Subjects in the best supportive care arm could receive defibrotide as rescue treatment for VOD. The median duration for rescue treatment was slightly shorter (16 days) than the recommended posology for severe VOD (minimum 21 days) in the defibrotide arm and 22 days in the BSC arm. As discussed above, it is assumed but should be verified that all subjects in the BSC arm who developed VOD as per the investigator's assessment were treated with defibrotide (**LoQ**).

For prior and concomitant medications, the presented data are in line with what could be expected for the population studied. It is however noted that concomitant medications were not consistently captured in the clinical database. This is not likely to have affected the incidence or assessment of VOD, for which no prophylactic treatment is approved, although ursodeoxycholic acid is often used (which was also used by more than 80% in the study in both treatment arms). For safety related to concomitant therapy, it is stated that concomitant medications were consistently captured in the pharmacovigilance database for reportable events. It is however unclear if treatment with other antithrombotic agents were consistently captured; since this is one of the safety concerns addressed by this study, the MAH should clarify whether subjects treated concomitantly with defibrotide and medications that increase the risk of haemorrhage were adequately captured, and provide outcome data in terms of VOD, bleeding events and TEAEs for these subjects (**LoQ**).

Adverse events

Treatment-emergent adverse events (TEAEs) are summarized by study phase and treatment arm in Table 12. During the prophylaxis phase of the study, all but 1 participant (DP arm) experienced 1 or more TEAEs. The proportion of participants with Grade 3 or 4 TEAEs, serious TEAEs, and TEAEs leading to death were similar between the 2 treatment arms. Ten participants in each treatment arm experienced a TEAE leading to death. Treatment-relatedness was based on relatedness to defibrotide only (ie, relatedness to BSC was not assessed), and none of the TEAEs leading to death in the DP arm were considered treatment-related. During the rescue phase of the study, all participants experienced 1 or more TEAEs. Treatment-emergent AEs leading to death were reported in 12 participants (48.0%) in the DP arm and 8 participants (25.8%) in the BSC arm. One participant in each treatment arm experienced a treatment-related TEAE leading to death.

Table 12. Treatment-emergent Adverse Events: Overall Summary – Safety Analysis Set

Study Phase		DP n (%)	BSC n (%)
Prophylaxis		**181**	**174**
	TEAE	180 (99.4)	174 (100.0)
	Grade 3 or 4 TEAE	155 (85.6)	151 (86.8)
	Serious TEAE	74 (40.9)	61 (35.1)
	Treatment-related TEAE	41 (22.7)	0
	Treatment-related Grade 3 or 4 TEAE	14 (7.7)	0
	Treatment-related serious TEAE	9 (5.0)	0
	TEAE leading to permanent discontinuation of study drug	21 (11.6)	2 (1.1)
	Treatment-related TEAE leading to permanent discontinuation of study drug	16 (8.8)	0
	TEAE leading to death	10 (5.5)	10 (5.7)
	Treatment-related TEAE leading to death	0	0
Rescue		**25**	**31**
	TEAE	25 (100.0)	31 (100.0)
	Grade 3 or 4 TEAE	18 (72.0)	27 (87.1)
	Serious TEAE	16 (64.0)	22 (71.0)
	Treatment-related TEAE	7 (28.0)	6 (19.4)
	Treatment-related Grade 3 or 4 TEAE	1 (4.0)	1 (3.2)
	Treatment-related Serious TEAE	1 (4.0)	2 (6.5)
	TEAE leading to permanent discontinuation of study drug	6 (24.0)	8 (25.8)
Study Phase		**DP n (%)**	**BSC n (%)**
	Treatment-related TEAE leading to permanent discontinuation of study drug	2 (8.0)	3 (9.7)
	TEAE leading to death	12 (48.0)	8 (25.8)
	Treatment-related TEAE leading to death	1 (4.0)	1 (3.2)

Abbreviations: BSC = Best Supportive Care; DP = Defibrotide Prophylaxis; TEAE = treatment-emergent adverse event.
Notes:
A TEAE is defined as any event with onset date on or after the first dose of study treatment or any ongoing event that worsens in severity after the date of the first dose of study treatment through the end of the protocol-specific reporting period.
Percentages were calculated with the number of participants in the Safety Analysis Set who entered the study phase in each arm as a denominator.
Source: Table 14.3.1.1

Adverse Events by System Organ Class and Preferred Term

The most common TEAEs (those occurring in ≥ 20% of participants in either treatment arm) are shown for each study phase by treatment arm in Table 13. The most common TEAEs during the prophylaxis phase in the DP arm were Pyrexia (111 participants [61.3%]), Nausea (109 participants [60.2%]), Diarrhoea and Stomatitis (105 participants [58.0%] each), and Vomiting (103 participants [56.9%]). The incidence of these TEAEs were similar in the 2 treatment arms. The most common TEAEs during the rescue phase were VOD (14 participants [56.0%] in the DP arm, and 18 participants [58.1%] in the BSC arm), Pyrexia (6 participants [24.0%] in the DP arm, and 11 participants [35.5%] in the BSC arm), and Diarrhoea (7 participants [28.0%] in the DP arm, and 7 participants [22.6%] in the BSC arm). Note that the incidence of VOD as an AE is not identical to the number of cases of VOD reported in the efficacy analyses, as both the primary and key secondary efficacy endpoints were based on EPAC diagnosis. Furthermore, not all cases of VOD may have been reported as an AE by the investigator, as VOD was already captured as part of the efficacy analyses in this study.

Table 13 Treatment-emergent Adverse Events Occurring in ⩾ 20% of Participants in Either Treatment Arm by Preferred Term – Safety Analysis Set

Study Phase	Preferred Term (MedDRA)	DP n (%)	BSC n (%)
Prophylaxis		**181**	**174**
	Number of Participants With at Least 1 TEAE	180 (99.4)	174 (100.0)
	Pyrexia	111 (61.3)	111 (63.8)
	Nausea	109 (60.2)	98 (56.3)
	Diarrhoea	105 (58.0)	106 (60.9)
	Stomatitis	105 (58.0)	116 (66.7)
	Vomiting	103 (56.9)	90 (51.7)
	Hypokalaemia	71 (39.2)	58 (33.3)
	Hypomagnesaemia	71 (39.2)	58 (33.3)
	Hypertension	68 (37.6)	51 (29.3)
	Abdominal pain	57 (31.5)	45 (25.9)
	Febrile neutropenia	52 (28.7)	61 (35.1)
	Decreased appetite	50 (27.6)	48 (27.6)
	Headache	49 (27.1)	35 (20.1)
	Anaemia	48 (26.5)	52 (29.9)
	Epistaxis	39 (21.5)	45 (25.9)
	Constipation	34 (18.8)	37 (21.3)
	Platelet count decreased	33 (18.2)	43 (24.7)
Rescue		**25**	**31**
	Number of Participants With at Least 1 TEAE	25 (100.0)	31 (100.0)
	Venoocclusive disease	14 (56.0)	18 (58.1)
	Constipation	7 (28.0)	2 (6.5)
	Diarrhoea	7 (28.0)	7 (22.6)
	Blood bilirubin increased	6 (24.0)	2 (6.5)
	Hypertension	6 (24.0)	6 (19.4)
	Hypokalaemia	6 (24.0)	6 (19.4)
	Pyrexia	6 (24.0)	11 (35.5)
	Abdominal distension	5 (20.0)	2 (6.5)
	Anaemia	5 (20.0)	3 (9.7)
	Platelet count decreased	5 (20.0)	2 (6.5)
	Pleural effusion	5 (20.0)	5 (16.1)
	Venoocclusive liver disease	5 (20.0)	3 (9.7)
	Vomiting	5 (20.0)	4 (12.9)
	Acute kidney injury	3 (12.0)	9 (29.0)
	Hypotension	3 (12.0)	9 (29.0)

Abbreviations: BSC = Best Supportive Care; DP = Defibrotide Prophylaxis; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; TEAE = treatment-emergent adverse event.

Notes:

Percentages were calculated with the number of participants in the Safety Analysis Set who entered the study phase in each arm as a denominator.

Adverse events were coded to PT using MedDRA 19.1.

Incidence was based on the number of participants, not on the number of events.

A TEAE is defined as any event with onset date on or after the first dose of study treatment or any ongoing event that worsens in severity after the date of the first dose of study treatment through the end of the protocol-specific reporting period.

PT were sorted by descending frequency in the DP arm and then alphabetically for those with the same frequency.

Source: Table 14.3.1.3

Treatment-emergent AEs are summarized by SOC and PT and by treatment arm by age subgroup (pediatrics, ≤16 years of age; adults, >16 years of age) in Table 14.3.1.4. While some AEs were more common in one age subgroup versus the other, there were no trends observed when comparing the DP arm to the BSC arm to suggest a safety concern in either age subgroup. *Assessor's comment: Table 14.3.1.4 presents a listing of all TEAEs divided by age group, using the total number of subjects in each treatment arm rather than the number of subjects in the age group as denominator for percentage calculations. No summary of the TEAEs in adults vs paediatric subjects has been provided.*

Treatment-related Adverse Events

Treatment-related (per the investigator) TEAEs that occurred in ≥ 2% of participants in either treatment arm are summarized by SOC and PT for each study phase by treatment arm in

Table 14. Assessments of treatment relatedness were made only in the DP arm during the prophylaxis phase.

During the prophylaxis phase, 41 participants (22.7%) in the DP arm experienced at least 1 treatment-related TEAE. Those that occurred in ≥ 2% of participants in the DP arm included Epistaxis (8 participants [4.4%]), and Haematochezia and Activated partial thromboplastin time prolonged (4 participants [2.2%] each). During the rescue phase, 7 participants (28.0%) in the DP arm and 6 participants (19.4%) in the BSC arm experienced at least 1 treatment-related TEAE. The most common treatment-related TEAEs during the rescue phase were Epistaxis (1 participant [4.0%] in the DP arm, and 2 participants [6.5%] in the BSC arm), Haematuria (1 participant [4.0%] in the DP arm, and 1 participant [3.2%] in the BSC arm), and VOD (1 participant [4.0%] in the DP arm, and 1 participant [3.2%] in the BSC arm).

Table 14 Treatment-related Treatment-emergent Adverse Events Occurring in ⩾ 2% of Participants in Either Treatment Arm by System Organ Class and Preferred Term – Safety Analysis Set

Study Phase	System Organ Class Preferred Term (MedDRA)	DP n (%)	BSC n (%)
Prophylaxis		**181**	**174**
	Number of participants with at least 1 treatment-related TEAE	41 (22.7)	0
	Gastrointestinal disorders	15 (8.3)	0
	Haematochezia	4 (2.2)	0
	Respiratory, thoracic and mediastinal disorders	14 (7.7)	0
	Epistaxis	8 (4.4)	0
	Investigations	5 (2.8)	0
	Activated partial thromboplastin time prolonged	4 (2.2)	0
Rescue		**25**	**31**
	Number of participants with at least 1 treatment-related TEAE	7 (28.0)	6 (19.4)
	Renal and urinary disorders	3 (12.0)	1 (3.2)
	Bladder spasm	1 (4.0)	0
	Haematuria	1 (4.0)	1 (3.2)
	Renal failure	1 (4.0)	0
	Gastrointestinal disorders	2 (8.0)	0
	Rectal haemorrhage	1 (4.0)	0
	Upper gastrointestinal haemorrhage	1 (4.0)	0
	Eye disorders	1 (4.0)	0
	Eye pain	1 (4.0)	0
	General disorders and administration site conditions	1 (4.0)	2 (6.5)
	Complication associated with device	1 (4.0)	0
	Catheter site haemorrhage	0	1 (3.2)
	Medical device site pain	0	1 (3.2)
	Immune system disorders	1 (4.0)	0
	Chronic graft versus host disease	1 (4.0)	0
	Injury, poisoning and procedural complications	1 (4.0)	0
	Excoriation	1 (4.0)	0
	Nervous system disorders	1 (4.0)	1 (3.2)
	Haemorrhage intracranial	1 (4.0)	0
	Cerebellar haemorrhage	0	1 (3.2)
	Psychiatric disorders	1 (4.0)	0
	Agitation	1 (4.0)	0
	Respiratory, thoracic and mediastinal disorders	1 (4.0)	2 (6.5)
	Epistaxis	1 (4.0)	2 (6.5)
	Skin and subcutaneous tissue disorders	1 (4.0)	0
	Rash generalised	1 (4.0)	0
	Vascular disorders	1 (4.0)	1 (3.2)
	Venoocclusive disease	1 (4.0)	1 (3.2)

Abbreviations: BSC = Best Supportive Care; DP = Defibrotide Prophylaxis; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event.

Notes:

Percentages were calculated with the number of participants in the Safety Analysis Set who entered the study phase in each arm as a denominator.

Adverse events were coded to SOC and PT using MedDRA 19.1.

Assessor's comment:

During the prophylaxis phase of the study, all but 1 participant experienced 1 or more TEAE. This could be expected, given the severity of underlying disease and concomitant treatment and procedure (HSCT). It is stated that 10 subjects in each treatment arm had an TEAE leading to death; none of these deaths were considered related to defibrotide in the defibrotide arm. The number of deaths appear however not fully consistent with other presented analyses, see also Deaths below.

During the rescue phase of the study, all participants experienced 1 or more TEAEs. Treatment-emergent AEs leading to death were reported in 12 participants (48.0%) in the DP arm and 8 participants (25.8%) in the BSC arm. In two subjects (assumed both to have been treated with defibrotide for rescue treatment) the TEAE leading to death was considered treatment-related.

For the paediatric population, there are some difficulties to assess the safety data based on the presentation provided. The MAH is asked to provide a summary of the TEAEs and the treatment-related TEAEs separated by children and adults using the number of children and adults respectively as the denominator when presenting percentages. Any differences between treatment groups as well as any differences between age groups should be addressed, including any implications for the labelling of adverse reactions (**LoQ**).

TEAEs judged by investigator as treatment-related were reported for defibrotide only. Based on the presentation of treatment-related TEAEs occurring in ≥ 2% of Participants (safety analysis set), the treatment-related TEAEs are considered in line with the known safety profile of defibrotide and the current label for Defitelio.

Serious adverse events

During the prophylaxis phase, 74 participants (40.9%) in the DP arm and 61 participants (35.1%) in the BSC arm experienced 1 or more serious TEAEs. The most common serious TEAEs during the prophylaxis phase in the DP arm were Pyrexia (10 participants [5.5%]) and Respiratory failure (6 participants [3.3%]). During the rescue phase, 16 participants (64.0%) in the DP arm and 22 participants (71.0%) in the BSC arm experienced 1 or more serious TEAEs. The most common serious TEAEs during the rescue phase were VOD (8 participants [32.0%] in the DP arm, and 5 participants [16.1%] in the BSC arm), Multiple organ dysfunction syndrome (3 participants [12.0%] in the DP arm, and 2 participants [6.5%] in the BSC arm), and Veno-occlusive liver disease (2 participants [8.0%] in the DP arm, and 3 participants [9.7%] in the BSC arm).

Table 15 Serious Treatment-emergent Adverse Events Occurring in ⩾ 2% of Participants in Either Treatment Arm by System Organ Class and Preferred Term – Safety Analysis Set

System Organ Class Preferred Term (MedDRA)	DP n (%)	BSC n (%)
Study Phase: Prophylaxis	**181**	**174**
Number of participants with at least 1 serious TEAE	74 (40.9)	61 (35.1)
Infections and infestations	20 (11.0)	19 (10.9)
Sepsis	4 (2.2)	3 (1.7)
Respiratory, thoracic and mediastinal disorders	13 (7.2)	9 (5.2)
Respiratory failure	6 (3.3)	3 (1.7)
Hypoxia	4 (2.2)	0
General disorders and administration site conditions	12 (6.6)	15 (8.6)
Pyrexia	10 (5.5)	12 (6.9)
Gastrointestinal disorders	8 (4.4)	10 (5.7)
Diarrhoea	0	4 (2.3)
Immune system disorders	8 (4.4)	5 (2.9)
Acute graft versus host disease in skin	4 (2.2)	1 (0.6)
Acute graft versus host disease in intestine	3 (1.7)	4 (2.3)
Study Phase: Rescue	**25**	**31**
Number of participants with at least 1 serious TEAE	16 (64.0)	22 (71.0)
Infections and infestations	9 (36.0)	10 (32.3)
Sepsis	2 (8.0)	2 (6.5)
BK virus infection	1 (4.0)	0
Bronchopulmonary aspergillosis	1 (4.0)	0
Candida sepsis	1 (4.0)	0
Device related infection	1 (4.0)	1 (3.2)
Pseudomonal sepsis	1 (4.0)	0
Septic shock	1 (4.0)	0
Staphylococcal bacteraemia	1 (4.0)	0
Adenovirus infection	0	1 (3.2)
Epstein-Barr virus infection	0	1 (3.2)
Meningoencephalitis herpetic	0	1 (3.2)
Pneumonia	0	3 (9.7)
Skin candida	0	1 (3.2)

System Organ Class Preferred Term (MedDRA)	DP n (%)	BSC n (%)
Vascular disorders	9 (36.0)	6 (19.4)
Venoocclusive disease	8 (32.0)	5 (16.1)
Hypotension	1 (4.0)	2 (6.5)
General disorders and administration site conditions	3 (12.0)	4 (12.9)
Multiple organ dysfunction syndrome	3 (12.0)	2 (6.5)
Pyrexia	0	2 (6.5)
Renal and urinary disorders	3 (12.0)	4 (12.9)
Acute kidney injury	1 (4.0)	2 (6.5)
Cystitis haemorrhagic	1 (4.0)	0
Nephropathy	1 (4.0)	0
Renal failure	0	1 (3.2)
Renal injury	0	1 (3.2)
Respiratory, thoracic and mediastinal disorders	3 (12.0)	6 (19.4)
Dyspnoea	1 (4.0)	0
Pleural effusion	1 (4.0)	0
Pulmonary oedema	1 (4.0)	0
Acute pulmonary oedema	0	1 (3.2)
Organising pneumonia	0	1 (3.2)
Respiratory distress	0	1 (3.2)
Respiratory failure	0	3 (9.7)
Gastrointestinal disorders	2 (8.0)	2 (6.5)
Colitis	1 (4.0)	0
Nausea	1 (4.0)	0
Diarrhoea	0	1 (3.2)
Haematochezia	0	1 (3.2)
Hepatobiliary disorders	2 (8.0)	3 (9.7)
Venoocclusive liver disease	2 (8.0)	3 (9.7)
Hepatic failure	0	1 (3.2)
Investigations	2 (8.0)	0
Blood creatinine increased	1 (4.0)	0
Neutrophil count decreased	1 (4.0)	0
Weight decreased	1 (4.0)	0

System Organ Class Preferred Term (MedDRA)	DP n (%)	BSC n (%)
Nervous system disorders	2 (8.0)	3 (9.7)
Haemorrhage intracranial	1 (4.0)	0
Leukoencephalopathy	1 (4.0)	0
Cerebellar haemorrhage	0	1 (3.2)
Cerebral haemorrhage	0	1 (3.2)
Seizure	0	1 (3.2)
Blood and lymphatic system disorders	1 (4.0)	2 (6.5)
Histiocytosis haematophagic	1 (4.0)	0
Thrombotic microangiopathy	0	2 (6.5)
Cardiac disorders	1 (4.0)	0
Cardiac arrest	1 (4.0)	0
Immune system disorders	1 (4.0)	0
Cytokine release syndrome	1 (4.0)	0
Injury, poisoning and procedural complications	1 (4.0)	1 (3.2)
Traumatic haematoma	1 (4.0)	0
Delayed engraftment	0	1 (3.2)
Subcutaneous haematoma	0	1 (3.2)
Metabolism and nutrition disorders	1 (4.0)	0
Hyperglycaemia	1 (4.0)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (3.2)
Acute lymphocytic leukaemia recurrent	0	1 (3.2)

Abbreviations: BSC = Best Supportive Care; DP = Defibrotide Prophylaxis; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event.
Notes:
Percentages were calculated with the number of participants in the Safety Analysis Set who entered the study phase in each arm as a denominator.
SOC and PT were sorted by descending frequency in the DP arm and then alphabetically for those with the same frequency.
Source: Module 5.3.5.4/Study 15-007 CSR/Table 17.

During the prophylaxis phase, 9 participants (5.0%) in the DP arm experienced a serious treatment-related TEAE, with the most common being Gastrointestinal haemorrhage (3 participants [1.7%]) and Haematemesis (2 participants [1.1%]). During the rescue phase, 1 participant (4.0%) in the DP arm experienced a serious treatment-related TEAE (Haemorrhage intracranial), and 2 participants (6.5%) in the BSC experienced a serious treatment-related TEAE (1 participant [3.2%] each with Cerebellar haemorrhage and VOD).

Assessor's comment:

There were slightly more subjects with at least 1 serious TEAE in the defibrotide arm as compared to BSC only, 74/181 (40.9%) vs 61/174 (35.1%) during the prophylaxis phase of the study. Of these, 9 participants (5.0%) in the defibrotide arm experienced a serious treatment-related TEAE, with the most common being gastrointestinal haemorrhage/haematemesis (in total 5 participants). To aid in further assessment and since the prophylaxis phase included observational time up to D180 post-HSCT (in subjects who did not develop VOD or died), the MAH is asked to present serious TEAEs occurring during the period when defibrotide was given for prophylaxis (up to D30 post-HSCT) by SOC and PT in both treatment arms, and divided by age groups (paediatric subjects vs adults). (LoQ)

During the rescue phase (assuming all 56 subjects included in this phase were treated with defibrotide), there were 16/25 or 64% TEAEs in patients randomised to prophylaxis with defibrotide and 22/31 or 71.0% TEAEs in patients randomised to prophylaxis with BSC. Of these, 3 participants experienced a serious treatment-related TEAE (1 each of intracranial haemorrhage, cerebellar haemorrhage and VOD). This is considered in line with the known safety profile of defibrotide, with cerebral haemorrhage being a labelled adverse reaction (frequency common) for Defitelio.

Deaths

Treatment-emergent AEs leading to death are summarized by SOC and PT for each study phase by treatment arm in Table 16.

During the prophylaxis phase, 10 participants (5.5%) in the DP arm and 10 participants (5.7%) in the BSC arm experienced at least 1 TEAE leading to death. The only TEAE leading to death that occurred in more than 1 participant overall was Respiratory failure (2 participants [1.1%] in each treatment arm).

During the rescue phase, 12 participants (48.0%) in the DP arm and 8 participants (25.8%) in the BSC arm experienced at least 1 TEAE leading to death. The most common TEAEs leading to death were VOD (4 participants [16.0%] in the DP arm, and 2 participants [6.5%] in the BSC arm), Multiple organ dysfunction syndrome (3 participants [12.0%] in the DP arm, and 2 participants [6.5%] in the BSC arm), Sepsis (1 participant [4.0%] in the DP arm, and 1 participant [3.2%] in the BSC arm), and Pneumonia (0 participants in the DP arm, and 2 participants [6.5%] in the BSC arm).

There were no treatment-related TEAEs leading to death during the prophylaxis phase of the study. During the rescue phase, 2 participants (1 in each treatment arm) experienced a treatment-related TEAE leading to death. These events included Haemorrhage intracranial (DP arm) and VOD (BSC arm).

Table 16. Treatment-emergent Adverse Events Leading to Death – Safety Analysis Set

Study Phase	System Organ Class Preferred Term (MedDRA)	DP n (%)	BSC n (%)
Prophylaxis		**181**	**174**
	Number of participants with at least 1 TEAE leading to death	10 (5.5)	10 (5.7)
	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (1.7)	3 (1.7)
	Acute leukaemia	1 (0.6)	0
	Acute lymphocytic leukaemia recurrent	1 (0.6)	0
	Acute myeloid leukaemia recurrent	1 (0.6)	0
	Burkitt's lymphoma	0	1 (0.6)
	Leukaemia	0	1 (0.6)
	Leukaemia recurrent	0	1 (0.6)
	Respiratory, thoracic and mediastinal disorders	3 (1.7)	3 (1.7)
	Respiratory failure	2 (1.1)	2 (1.1)
	Acute respiratory distress syndrome	1 (0.6)	0
	Pulmonary haemorrhage	0	1 (0.6)
	Blood and lymphatic system disorders	1 (0.6)	0
	Thrombotic microangiopathy	1 (0.6)	0
	Gastrointestinal disorders	1 (0.6)	0
	Abdominal pain	1 (0.6)	0
	Infections and infestations	1 (0.6)	2 (1.1)
	Bacterial infection	1 (0.6)	0
	Infection	1 (0.6)	0
	Pneumonia	0	1 (0.6)
	Sepsis	0	1 (0.6)
	Nervous system disorders	1 (0.6)	0
	Posterior reversible encephalopathy syndrome	1 (0.6)	0
	Immune system disorders	0	1 (0.6)
	Acute graft versus host disease in intestine	0	1 (0.6)
	Acute graft versus host disease in liver	0	1 (0.6)
	Vascular disorders	0	1 (0.6)
	Air embolism	0	1 (0.6)
Rescue		**25**	**31**
	Number of participants with at least 1 TEAE leading to death	12 (48.0)	8 (25.8)
	Infections and infestations	5 (20.0)	4 (12.9)
	Bronchopulmonary aspergillosis	1 (4.0)	0
	Candida sepsis	1 (4.0)	0
	Pseudomonal sepsis	1 (4.0)	0
	Sepsis	1 (4.0)	1 (3.2)
	Septic shock	1 (4.0)	0
	Adenovirus infection	0	1 (3.2)
	Pneumonia	0	2 (6.5)
	Vascular disorders	4 (16.0)	2 (6.5)
	Venoocclusive disease	4 (16.0)	2 (6.5)
	General disorders and administration site conditions	3 (12.0)	2 (6.5)
	Multiple organ dysfunction syndrome	3 (12.0)	2 (6.5)
	Nervous system disorders	2 (8.0)	0

Study Phase	System Organ Class Preferred Term (MedDRA)	DP n (%)	BSC n (%)
	Haemorrhage intracranial	1 (4.0)	0
	Leukoencephalopathy	1 (4.0)	0
	Blood and lymphatic system disorders	1 (4.0)	0
	Histiocytosis haematophagic	1 (4.0)	0
	Cardiac disorders	1 (4.0)	0
	Cardiac arrest	1 (4.0)	0
	Renal and urinary disorders	1 (4.0)	0
	Acute kidney injury	1 (4.0)	0
	Respiratory, thoracic and mediastinal disorders	0	1 (3.2)
	Respiratory failure	0	1 (3.2)

Abbreviations: BSC = Best Supportive Care; DP = Defibrotide Prophylaxis; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event.
Notes:
Percentages were calculated with the number of participants in the Safety Analysis Set who entered the study phase in each arm as a denominator.
Adverse events were coded to SOC and PT using MedDRA 19.1.
Incidence was based on the number of participants, not on the number of events.
A TEAE is defined as any event with onset date on or after the first dose of study treatment or any ongoing event that worsens in severity after the date of the first dose of study treatment through the end of the protocol-specific reporting period.
SOC and PT were sorted by descending frequency in the DP arm and then alphabetically for those with the same frequency.
Source: Table 14.3.1.14

Post-hoc analyses of deaths

All deaths reported during the study, including those that occurred outside of the protocol-defined AE reporting period, by Day +30, Day +100, and Day +180 post-HSCT are summarized by treatment arm in Table 17. For the participants who died by Day +30 post-HSCT, the cause of death was primarily due to AEs expected in patients undergoing transplant. By Day +100 post-HSCT, an additional 18 participants in the DP arm and 15 participants in the BSC arm died. From Day +100 post-HSCT to Day +180 post-HSCT, 7 deaths in the DP arm and 10 deaths in the BSC arm were reported.

Table 17 All Deaths by Day +180 Post-HSCT – ITT Analysis Set

	Variable	DP (N=190)	BSC (N=182)
Death by Day +30 post-HSCT	Number of deaths, n (%)	10 (5.7)	5 (2.9)
	Primary cause of death, n (%)		
	Disease progression	0	0
	Disease relapse	0	0
	Adverse event	9 (90.0)	5 (100.0)
	Unknown	0	0
	Other, specify	1 (10.0)	0
Death by Day +100 post-HSCT	Number of deaths, n (%)	28 (17.5)	20 (12.7)
	Primary cause of death, n (%)		
	Disease progression	2 (7.1)	2 (10.0)
	Disease relapse	2 (7.1)	0
	Adverse event	21 (75.0)	18 (90.0)
	Unknown	0	0
	Other, specify	3 (10.7)	0
Death by Day +180 post-HSCT	Number of deaths, n (%)	35 (32.1)	30 (29.4)
	Primary cause of death, n (%)		
	Disease progression	5 (14.3)	3 (10.0)
	Disease relapse	3 (8.6)	2 (6.7)
	Adverse event	23 (65.7)	23 (76.7)
	Unknown	0	0
	Other, specify	4 (11.4)	2 (6.7)

Abbreviations: BSC = Best Supportive Care; DP = Defibrotide Prophylaxis; HSCT = hematopoietic stem cell transplant; ITT = Intent-to-Treat.

Notes:

For Number of Deaths, percentages were calculated based on the number of participants who have died by and who were still alive on certain post-HSCT day (Day +30 post-HSCT, Day +100 post-HSCT, or Day +180 post-HSCT) within each treatment arm from the ITT Analysis Set as a denominator.

For Primary Cause of Death, percentages were calculated based on the Number of Deaths within each treatment arm from the ITT Analysis Set as a denominator.

Source: Table 14.2.5

Assessor's comment:

The numbers of deaths during study 15-007 as presented in the different analyses cannot be followed.

According to the definition of 'Prophylaxis Phase' for safety evaluations, this phase was defined as the period between baseline and start date of rescue defibrotide, if applicable, or the period between baseline and Day +180 post-HSCT if no VOD occurred. According to these data (Table 16 above), there were 10 participants in each treatment arm who suffered at least one TEAE leading to death during the prophylaxis phase, and 12 subjects in the defibrotide arm vs 8 subjects in the BSC arm who died due to TEAE during the rescue phase. Recurrent malignancies appear to have been included as a TEAE, and it is unclear if there were additional subjects who died during these phases (that were not reported as TEAEs).

In the post-hoc analysis of deaths up to day 180 post-HSCT, however, 10 subjects in the defibrotide arm and 5 subjects in the BSC arm died by Day +30 post-HSCT (which was the time period during which defibrotide was administered in the defibrotide arm, and the time point for evaluation of the primary efficacy outcome). Up to day +180 post-HSCT, 35/190 subjects died in the defibrotide arm and 30/182 in the BSC arm out of which 23 deaths in each treatment arm had adverse events as primary cause of death. The MAH is asked to clarify why only 10 of these deaths were included in the presentation of TEAE leading to death during the prophylaxis phase (even adding those who were diagnosed with VOD and died due to adverse event, the figures are not congruent) (**LoQ**). In addition, the MAH should provide the total number of deaths up to day 30-post-HSCT divided by age groups (paediatric subjects vs adults) including causes of death (**LoQ**).

Adverse Events of Special Interest

Adverse events of special interest included events in categories of pulmonary haemorrhage, gastrointestinal bleeding, and hypersensitivity reactions. For either treatment arm, participant narratives were written for AESIs meeting any of the following criteria (Section 11): Grade >1 AESI or any grade if more than 1 AESI occurred, met serious criteria, assessed by the investigator as related to study treatment, led to a change in study drug (withdrawn or interrupted), and/or led to the participant discontinuing the study.

Pulmonary Haemorrhage

In the prophylaxis phase, 44 participants (24.3%) in the DP arm and 46 participants (26.4%) in the BSC arm experienced 1 or more TEAEs of special interest in the category of pulmonary haemorrhage (Table 14.3.1.17). The majority of the AEs reported were of Epistaxis in both the DP and BSC arms (39 participants [21.5%] and 45 participants [25.9%], respectively). Excluding Epistaxis, the most common TEAEs in the DP arm were Haemoptysis (3 participants [1.7%]), Respiratory tract haemorrhage (2 participants [1.1%]), and Bronchial haemorrhage, Pulmonary alveolar haemorrhage, and Pulmonary haemorrhage (1 participant [0.6%] each). In the BSC arm, excluding Epistaxis, 1 participant (0.6%) experienced Pulmonary haemorrhage. In both treatment arms, the proportion of participants who experienced 1 or more TEAEs of special interest in the category of pulmonary haemorrhage during the prophylaxis phase was similar in the paediatric and adult subgroups.

In the rescue phase, 4 participants (16.0%) in the DP arm and 6 participants (19.4%) in the BSC arm experienced 1 or more TEAEs of special interest in the category of pulmonary haemorrhage (Table 14.3.1.17). In the DP arm, these included 3 participants (12.0%) with Epistaxis (2 paediatrics and 1 adult) and 1 participant (4.0%) with Haemoptysis (paediatric). In the BSC arm, these included 6 participants (19.4%) with Epistaxis (5 paediatrics and 1 adult).

Gastrointestinal Bleeding

In the prophylaxis phase, 16 participants (8.8%) in the DP arm and 14 participants (8.0%) in the BSC arm experienced 1 or more TEAEs of special interest in the category of gastrointestinal bleeding (Table 14.3.1.19). In both treatment arms of the prophylaxis phase, TEAEs of special interest in the category of gastrointestinal bleeding were experienced by a higher incidence of paediatric participants than adult participants (DP arm: 10 paediatric participants [5.5%], and 6 adult participants [3.3%]; BSC arm: 10 paediatric participants [5.7%], and 4 adult participants [2.3%]).

In the rescue phase, 4 participants (16.0%) in the DP arm and 6 participants (19.4%) in the BSC arm experienced 1 or more TEAEs of special interest in the category of gastrointestinal bleeding.

Hypersensitivity Reactions

In the prophylaxis phase, 91 participants (50.3%) in the DP arm and 78 participants (44.8%) in the BSC arm experienced 1 or more TEAEs of special interest in the category of hypersensitivity reactions. In both treatment arms of the prophylaxis phase, TEAEs of special interest in the category of hypersensitivity reactions were experienced by a higher incidence of paediatric participants than adult participants (DP arm: 56 paediatric participants [30.9%], and 35 adult participants [19.3%]; BSC arm: 46 paediatric participants [26.4%], and 32 adult participants [18.4%]).

In the rescue phase, 8 participants (32.0%) in the DP arm and 1 participant (3.2%) in the BSC arm experienced 1 or more TEAEs of special interest in the category of hypersensitivity reactions.

Assessor's comment:

For adverse events of special interest, there was no difference in pulmonary or gastrointestinal haemorrhage between treatment arms during the prophylaxis phase.

An imbalance is noted for hypersensitivity reactions, reported by 91 participants (50.3%) in the defibrotide arm and 78 participants (44.8%) in the BSC arm during the prophylaxis phase. A more pronounced difference is noted for the rescue phase, reported in 8 participants (32.0%) in the defibrotide arm and 1 participant (3.2%) in the BSC arm.

For all three adverse events of special interest (which are also labelled adverse reactions for Defitelio), the reported event rates during rescue treatment appear higher than what would be expected based on the current label. The MAH should discuss these data in relation to the labelled frequencies and propose any label updates if warranted (**LoQ**). Also, since immunogenicity was an exploratory endpoint for which no data have been provided, given the difference between prophylaxis treatment arms in subjects who developed VOD and were treated with defibrotide, the MAH is asked to provide the immunogenicity data (**LoQ**).

Other Safety Evaluations and Observations related to safety

Vital sign results and changes from baseline are summarized by treatment arm for each phase of the study in Table 14.3.3.1. A shift table summarizing changes from baseline between low, normal, and high values at each assessment is provided in Table 14.3.3.3, and maximum increases/decreases from baseline in systolic and diastolic blood pressure are summarized in Table 14.3.3.2. There were no trends in either treatment arm suggesting a safety concern. Most participants had normal values at baseline, and values remained normal throughout the study.

Graft-versus-Host Disease

Of the participants with allogenic donors, the proportion who were diagnosed with chronic GvHD by Day +180 post-HSCT were similar between the 2 treatment arms (14 of 147 participants [9.5%] in the DP arm, and 12 of 142 participants [8.5%] in the BSC arm). The proportion diagnosed with acute GvHD (Grade I-IV) by Day +180 post-HSCT was also similar between the 2 treatment arms (41 of 147 participants [27.9%] in the DP arm, and 49 of 142 participants [34.5%] in the BSC arm).

Graft Failure and Time to Neutrophil and Platelet Engraftment

Neutrophil engraftment was achieved by 156 participants (86.2%) in the DP arm and 162 participants (93.1%) in the BSC arm by Day +180 post-HSCT. The KM estimate (95% CI) of the median time to neutrophil engraftment is 17.0 (15.0, 18.0) days in the DP arm and 16.0 (14.0, 17.0) days in the BSC arm.

Platelet engraftment was achieved by 154 participants (85.1%) in the DP arm and 163 participants (93.7%) in the BSC arm by Day +180 post-HSCT. The KM estimate (95% CI) of the median time to platelet engraftment is 24.0 (22.0, 26.0) days in the DP arm and 25.0 (21.0, 27.0) days in the BSC arm. Graft failure occurred in 4 participants (2.2%) in the DP arm and 3 participants (1.7%) in the BSC arm during the prophylaxis phase. During the rescue phase, 4 participants (16.0%) in the DP arm and 3 participants (9.7%) in the BSC arm experienced graft failure.

Karnofsky and Lansky Performance Scores

Karnofsky and Lansky performance scores were high at baseline (median scores of 90.0 for both treatment arms and for both the Karnofsky and Lansky scores), indicating high functional status. Post-HSCT scores were high or moderate during the prophylaxis phase and were generally similar between the 2 treatment arms. Scores were lower during the rescue phase, which was expected considering these participants had developed VOD. Karnofsky and Lansky performance status is summarized by participant in Listing 16.2.15.

Abdominal Ultrasound

Abdominal ultrasound results are provided by participant in Listing 16.2.16.

Hospital Resource Utilization

Duration of hospital stay was similar between the 2 treatment arms, with a median (min, max) hospital stay of 45.0 (1, 211) days in the DP arm and 47.5 (16, 193) days in the BSC arm (Table 14.2.3.1). Resource utilization, including blood transfusion, ventilator use, dialysis, and number of biopsies, was generally comparable between the 2 treatment arms. Details on hospital and ICU stay and on inpatient resource utilization are provided by participant in Listings 16.2.17.1 and 16.2.17.2, respectively.

Health-related Quality of Life

For participants ≥ 16 years of age, EQ-5D-5L scores are summarized in Table 14.2.4.1. Across the dimensions of the EQ-5D-5L, conditions were unchanged from baseline in the majority of participants at Day +180 post-HSCT (Table 14.2.4.2). Similar results were observed in the 2 treatment arms. Post-HSCT EQ VAS scores and change from baseline were similar between the 2 treatment arms (Table 14.2.4.3).

For participants ≥ 8 to ≤ 15 years of age and ≥ 4 to ≤ 7 years of age, EQ-5D-Y scores are summarized in Tables 14.2.4.4 and 14.2.4.7, respectively. Across the dimensions of the EQ-5D-Y in both paediatric age groups, conditions were unchanged from baseline in the majority of participants at Day +180 post-HSCT, with the exception of anxiety in the ≥ 8 to ≤ 15 age group (Tables 14.2.4.5 and 14.2.4.8). In

this age group, a similar proportion of participants had improved anxiety compared to unchanged anxiety (Table 14.2.4.5). In both paediatric age groups, similar results were observed in the 2 treatment arms. In both paediatric age groups, post-HSCT EQ VAS scores and change from baseline were similar between the 2 treatment arms (Tables 14.2.4.6 and 14.2.4.9).

Assessor's comment:

For vital signs, the presentation of data is currently not sufficient. Of note, hypotension is one of the safety concerns addressed by this study. The MAH should summarise all vital sign variables recorded and present these for the respective treatment group at baseline and at day 30 post-HSCT for the prophylaxis period, and at diagnosis of VOD and at day +30 post-VOD treatment for the rescue treatment period. These data should be provided for the overall study population (safety analysis set) and divided by age groups (paediatric subjects vs adults). (**LoQ**)

Chronic GvHD was diagnosed in slightly more participants with allogenic donors in the defibrotide arm as compared to the BSC arm by Day +180 post-HSCT (14/147 participants [9.5%] in the defibrotide arm, and 12/142 participants [8.5%] in the BSC arm). On the contrary, acute GvHD (Grade I-IV) by Day +180 post-HSCT was diagnosed in 41/147 participants [27.9%] in the defibrotide arm, and 49 of 142 participants [34.5%] in the BSC arm. GvHD not adjudicated by the EPAC but based on investigators' assessments.

Slightly lower engraftment occurred in the defibrotide arm: neutrophil engraftment was achieved by 156/181 participants (86.2%) in the defibrotide arm and 162/174 participants (93.1%) in the BSC arm by Day +180 post-HSCT; platelet engraftment was achieved by 154 participants (85.1%) in the DP arm and 163 participants (93.7%) in the BSC arm by Day +180 post-HSCT. During the rescue phase, 4 participants (16.0%) in the DP arm and 3 participants (9.7%) in the BSC arm experienced graft failure. The MAH is asked to discuss these findings on graft failure during the rescue phase in more detail, including any possible relation to defibrotide (**LoQ**).

There were no differences between treatment arms regarding Karnofsky and Lansky performance scores, hospital resource utilization or health-related quality of life. For abdominal ultrasound results, no summary of data has been provided; the MAH is asked to provide a summary of the findings in each treatment group, for the overall study population (safety analysis set) and divided by age groups (paediatric subjects vs adults). (**LoQ**)

Laboratory findings

Overall, no clinically meaningful changes over time were observed for any haematology or chemistry laboratory parameter, and there were no notable differences in laboratory results between treatment arms. Table of selected laboratory results from baseline during each study phase is provided for the DP and BSC treatment arms in Tables 14.3.2.4.1 and 14.3.2.4.2, respectively.

Haematology

Given the condition of patients receiving HSCT, abnormal haematology parameters were expected during the course of the study. As such, shifts in haematology parameters to Grade 3 and Grade 4 were observed during both the prophylaxis and rescue phases (Tables 14.3.2.4.1 and 14.3.2.4.2), but the quantitative nature of the shifts was similar between treatment arms (Table 14.3.2.1). Mean changes from baseline were similar between the treatment arms over time (Table 14.3.2.1).

Chemistry

Shifts in chemistry parameters were similar between treatment arms during the prophylaxis and rescue phases of the study (Tables 14.3.2.4.1 and 14.3.2.4.2). Mean changes from baseline were also similar between the treatment arms over time (Table 14.3.2.2).

Coagulation

Mean changes from baseline in coagulation parameters were similar between the treatment arms over time (Table 14.3.2.3).

Assessor's comment:

For laboratory findings, the presentation of data is currently not sufficient. Coagulopathy is one of the safety concerns addressed by this study, and also the data on haematology and chemistry are of interest in line with the safety concerns (see below). The MAH should summarise the variables recorded for the laboratory findings and present these for the respective treatment group at baseline and at day 30 post-HSCT for the prophylaxis period, and at diagnosis of VOD and at day +30 post-VOD treatment for the rescue treatment period. These data should be provided for the overall study population (safety analysis set) and divided by age groups (paediatric subjects vs adults). (**LoQ**)

Immunological events

The immunogenicity analysis will be reported separately.

Assessor's comment:

Immunogenicity is one of the safety concerns addressed by this study, of particular interest given the hypersensitivity data (see above). The immunogenicity analyses should be provided (**LoQ**).

Discontinuations due to adverse events

During the prophylaxis phase, 21 participants (11.6%) in the DP arm and 2 participants (1.1%) in the BSC arm experienced at least 1 TEAE leading to treatment discontinuation. Of note, the 2 participants in the BSC arm, who were captured as having a TEAE leading to discontinuation during the prophylaxis phase, did not receive defibrotide during this time; the action taken with study treatment in these cases should have been captured as "not applicable". Treatment-emergent AEs leading to treatment discontinuation that occurred in more than 1 participant overall during the prophylaxis phase included Epistaxis, n = 3 [1.7%] and Haemoptysis, Gastrointestinal haemorrhage, and Activated partial thromboplastin time, each n = 2 [1.1%]. Of the 21 participants in the DP arm with a TEAE leading to discontinuation, a majority (n = 16; 76.2%) had the event assessed as treatment related. The apparent imbalance in discontinuation due to TEAEs between the DP arm and the BSC arm is explained by the fact that participants in the BSC arm did not have TEAEs assessed as leading to treatment discontinuation during the prophylaxis phase as they did not receive defibrotide.

During the rescue phase, a similar proportion of participants in the DP arm (24.0%) compared to the BSC arm (25.8%) experienced at least 1 TEAE leading to discontinuation. During this phase, Epistaxis was the only TEAE leading to treatment discontinuation that occurred in more than 1 participant overall (none in the DP arm; n = 2 [6.5%] BSC arm). Of the participants with a TEAE leading to discontinuation during the rescue phase, a similar percentage had the TEAE leading to discontinuation assessed as treatment related: n = 2 [8.0%] in the DP arm (n = 1 each with Rectal haemorrhage and Haemorrhage intracranial), and n = 3 (9.7%) in the BSC arm (n = 2 [6.5%] with Epistaxis and n = 1 [3.2%] with Haematuria).

Assessor's comment:

Discontinuations due to adverse events were applicable for the defibrotide arm only during the prophylaxis period. In the defibrotide arm, 21 participants (11.6%) discontinued defibrotide due to TEAEs, primarily due to bleeding events; only 16 of these TEAEs were however considered treatment-related. This discrepancy is not further pursued.

During the rescue phase when assumably all participants received defibrotide, 6/25 (24.0%) in the defibrotide prophylaxis arm and 8/31 (25.8%) in the BSC arm had at least 1 TEAE leading to treatment discontinuation. Of these 14 participants, 7 had bleeding TEAEs.

7.3. Discussion

The main safety concern is the numerical imbalance in favour of best supportive care for VOD-free survival both during the prophylaxis period of study 15-007 and more pronounced during the rescue treatment period. The population studied is similar to the population covered by the approved indication and these data are in line with previous prophylaxis data indicating increased mortality with defibrotide treatment, especially in the paediatric population. The MAH should discuss the apparent imbalance in mortality with defibrotide treatment, in relation to the approved indication (**LoQ**).

For the safety analyses, 2 study phases were defined with respect to the administration of rescue defibrotide:

•Prophylaxis Phase – For the overall safety population, this phase was defined as the period between baseline and start date of rescue defibrotide, if applicable, or the period between baseline and Day +180 post-HSCT if no VOD occurred. (End date of Prophylaxis Phase = start date of rescue defibrotide – 1 or Day +180 post-HSCT if no VOD occurred)

•Treatment Phase – For the subset of patients in the safety population who developed VOD and received rescue defibrotide, this phase is defined as the period between start date of rescue defibrotide and Day +180 post-HSCT. (Start date of Treatment Phase = start date of rescue defibrotide)

Of note, however, during the 'prophylaxis phase', defibrotide was only administered up to at maximum Day +30 post-HSCT. Given the severity of underlying disease and concomitant treatments as well as the short half-life of defibrotide, safety data during and shortly after the administration of defibrotide are considered to have the strongest clinical impact. For the treatment phase, it is assumed but should be verified that all subjects in the BSC arm who developed VOD as per the investigator's assessment were treated with defibrotide (**LoQ**).

For prior and concomitant medications, the presented data are in line with what could be expected for the population studied. It is however noted that concomitant medications were not consistently captured in the clinical database. This is not likely to have affected the incidence or assessment of VOD, for which no prophylactic treatment is approved, although ursodeoxycholic acid is often used (which was also used by more than 80% in the study in both treatment arms). For safety related to concomitant therapy, it is stated that concomitant medications were consistently captured in the pharmacovigilance database for reportable events. It is however unclear if treatment with other medications that could increase the risk of bleeding were consistently captured; since this is one of the safety concerns addressed by this study, the MAH should clarify whether subjects treated concomitantly with defibrotide and medications that increase the risk of haemorrhage were adequately captured, and provide outcome data in terms of VOD, bleeding events and TEAEs for these subjects (**LoQ**).

Adverse events

During the prophylaxis phase of the study, all but 1 participant experienced 1 or more TEAE. This could be expected, given the severity of underlying disease and concomitant treatment and procedure (HSCT). The majority of TEAEs were not considered treatment-related. During the rescue phase of the study, all participants experienced 1 or more TEAEs. Treatment-emergent AEs leading to death were reported in 12 participants (48.0%) in the DP arm and 8 participants (25.8%) in the BSC arm. In two subjects (assumed both to have been treated with defibrotide for rescue treatment) the TEAE leading to death was considered treatment-related.

There were slightly more subjects with at least 1 serious TEAE in the defibrotide arm as compared to BSC only, 74/181 (40.9%) vs 61/174 (35.1%) during the prophylaxis phase of the study. Of these, 9 participants (5.0%) in the defibrotide arm experienced a serious treatment-related TEAE, with the most common being gastrointestinal haemorrhage/haematemesis (5 participants in total). To aid in further assessment and since the prophylaxis phase included observational time up to D180 post-HSCT (in subjects who did not develop VOD or died), the MAH is asked to present serious TEAEs occurring during the period when defibrotide was given for prophylaxis (up to D30 post-HSCT) by SOC and PT in both treatment arms, and divided by age groups (paediatric subjects vs adults). (**LoQ**)

During the rescue phase (assuming all 56 subjects included in this phase were treated with defibrotide), there were 16/25 or 64% TEAEs in patients randomised to prophylaxis with defibrotide and 22/31 or 71.0% TEAEs in patients randomised to prophylaxis with BSC. Of these, 3 participants experienced a serious treatment-related TEAE (1 each of intracranial haemorrhage, cerebellar haemorrhage and VOD). This is considered in line with the known safety profile of defibrotide, with cerebral haemorrhage being a labelled adverse reaction (frequency common) for Defitelio.

For the paediatric population, there are some difficulties to assess the safety data based on the presentation provided. The MAH is asked to provide a summary of the TEAEs and the treatment-related TEAEs separated by children and adults using the number of children and adults respectively as the denominator when presenting percentages. Any differences between treatment groups as well as any differences between age groups should be addressed, including any implications for the labelling of adverse reactions (**LoQ**).

For adverse events of special interest, there was no difference in pulmonary or gastrointestinal haemorrhage between treatment arms during the prophylaxis phase.

An imbalance is noted for hypersensitivity reactions, reported by 91 participants (50.3%) in the defibrotide arm and 78 participants (44.8%) in the BSC arm during the prophylaxis phase. A more pronounced difference is noted for the rescue phase, reported in 8 participants (32.0%) in the defibrotide arm and 1 participant (3.2%) in the BSC arm.

For all three adverse events of special interest (which are also labelled adverse reactions for Defitelio), the reported event rates during rescue treatment appear higher than what would be expected based on the current label. Haemorrhage is one of the safety concerns to be further characterised by this study. The MAH should discuss these data in relation to the labelled frequencies and propose any label updates if warranted (LoQ). Also, immunogenicity is also a safety concern to be further addressed by this study; given the difference in hypersensitivity between prophylaxis treatment arms (defibrotide vs BSC) in subjects who developed VOD and were treated with defibrotide, the MAH should provide the immunogenicity data that were captured but have not been presented (**LoQ**).

Discontinuations due to adverse events were applicable for the defibrotide arm only during the prophylaxis period. In the defibrotide arm, 21 participants (11.6%) discontinued defibrotide due to

TEAEs, primarily due to bleeding events; only 16 of these TEAEs were however considered treatment-related. This discrepancy is not further pursued.

During the rescue phase when assumably all participants received defibrotide, 6/25 (24.0%) in the defibrotide prophylaxis arm and 8/31 (25.8%) in the BSC arm had at least 1 TEAE leading to treatment discontinuation. Of these 14 participants, 7 had bleeding TEAEs.

Deaths

Clarifications are warranted regarding the numbers of deaths during study 15-007 and the assessment of treatment-relatedness:

According to the definition of 'Prophylaxis Phase' for safety evaluations, this phase was defined as the period between baseline and start date of rescue defibrotide, if applicable, or the period between baseline and Day +180 post-HSCT if no VOD occurred. According to these data (Table 15 above), there were 10 participants in each treatment arm who suffered at least one TEAE leading to death during the prophylaxis phase, and 12 subjects in the defibrotide arm vs 8 subjects in the BSC arm who died due to TEAE during the rescue phase. Recurrent malignancies appear to have been included as a TEAE, and it is unclear if there were additional subjects who died during these phases (that were not reported as TEAEs).

In the post-hoc analysis of deaths up to day 180 post-HSCT, however, 10 subjects in the defibrotide arm and 5 subjects in the BSC arm died by Day +30 post-HSCT (which was the time period during which defibrotide was administered in the defibrotide arm, and the time point for evaluation of the primary efficacy outcome). Up to day +180 post-HSCT, 35/190 subjects died in the defibrotide arm and 30/182 in the BSC arm out of which 23 deaths in each treatment arm had adverse events as primary cause of death. The MAH is asked to clarify why only 10 of these deaths were included in the presentation of TEAE leading to death during the prophylaxis phase (even adding those who were diagnosed with VOD and died due to adverse event, the figures are not congruent) (LoQ). In addition, the MAH should provide the total number of deaths up to day 30-post-HSCT divided by age groups (paediatric subjects vs adults) including causes of death (**LoQ**).

Other Safety Evaluations and Laboratory findings

For vital signs, the presentation of data is currently not sufficient. Of note, hypotension is one of the safety concerns addressed by this study. The MAH should summarise all vital sign variables recorded and present these for the respective treatment group at baseline and at day 30 post-HSCT for the prophylaxis period, and at diagnosis of VOD and at day +30 post-VOD treatment for the rescue treatment period. These data should be provided for the overall study population (safety analysis set) and divided by age groups (paediatric subjects vs adults). (**LoQ**)

Chronic GvHD was diagnosed in slightly more participants with allogenic donors in the defibrotide arm as compared to the BSC arm by Day +180 post-HSCT (14/147 participants [9.5%] in the defibrotide arm, and 12/142 participants [8.5%] in the BSC arm). On the contrary, acute GvHD (Grade I-IV) by Day +180 post-HSCT was diagnosed in 41/147 participants [27.9%] in the defibrotide arm, and 49 of 142 participants [34.5%] in the BSC arm. GvHD not adjudicated by the EPAC but based on investigators' assessments.

Slightly lower engraftment occurred in the defibrotide arm: neutrophil engraftment was achieved by 156/181 participants (86.2%) in the defibrotide arm and 162/174 participants (93.1%) in the BSC arm by Day +180 post-HSCT; platelet engraftment was achieved by 154 participants (85.1%) in the DP arm and 163 participants (93.7%) in the BSC arm by Day +180 post-HSCT. During the rescue phase, 4 participants (16.0%) in the DP arm and 3 participants (9.7%) in the BSC arm experienced graft

failure. The MAH is asked to discuss these findings on graft failure during the rescue phase in more detail, including any possible relation to defibrotide (**LoQ**).

There were no differences between treatment arms regarding Karnofsky and Lansky performance scores, hospital resource utilization or health-related quality of life. For abdominal ultrasound results, no summary of data has been provided; the MAH is asked to provide a summary of the findings in each treatment group, for the overall study population (safety analysis set) and divided by age groups (paediatric subjects vs adults). (**LoQ**)

For laboratory findings, the presentation of data is currently not sufficient. Coagulopathy is one of the safety concerns addressed by this study. The MAH should summarise the variables recorded for the laboratory findings and present these for the respective treatment group at baseline and at day 30 post-HSCT for the prophylaxis period, and at diagnosis of VOD and at day +30 post-VOD treatment for the rescue treatment period. These data should be provided for the overall study population (safety analysis set) and divided by age groups (paediatric subjects vs adults). (**LoQ**)

Rapporteur's conclusion on safety

Several clarifications of the safety data are warranted before any conclusion on the safety profile of defibrotide in study 15-007 can be made. Although this study primarily addressed prophylaxis of VOD, the safety data are of importance also for the approved indication, since defibrotide was used for VOD rescue treatment (in line with the approved indication albeit for severe VOD only) and since the population studied (post-HSCT) is similar to the population covered by the approved indication. The main safety concern is the numerical imbalance in favour of best supportive care for VOD-free survival both during the prophylaxis period of study 15-007 and more pronounced during the rescue treatment period; an in-depth discussion on this imbalance in relation to the approved indication and in light of previous data is warranted (**MO**).

Study 15-007 is a Category 2 study in the Defitelio RMP, addressing the following safety concerns: Haemorrhage, Hypotension, Coagulopathy, Immunogenicity, Thromboembolic events, Patients treated concomitantly with defibrotide and medications that increase the risk of haemorrhage (including the newer oral anti-coagulants direct thrombin and factor Xa inhibitors), Patients with pre-existing liver or severe renal insufficiency (aetiologies other than VOD) and Patients with intrinsic lung disease. No clear presentation of data relating to each of these safety concerns has been provided; this is expected with the response to the RSI.

Overall, the safety data from study 15-007 that are considered of most relevance are the data from the prophylaxis period when defibrotide was administered to subjects in the defibrotide arm (up to Day +30 post-HSCT), and the data from the rescue treatment period (when assumably all subjects diagnosed with VOD by investigators received defibrotide). Serious treatment-related TEAEs during both treatment periods include serious bleeding events, which could be expected given the known safety profile of defibrotide. However, it should be clarified when in the study and in what age groups (paediatric subjects vs adults) serious TEAEs occurred, given that the safety profile could differ between children and adults, and since the data on efficacy indicate worse outcome in the defibrotide arm especially in the paediatric population.

Additional clarifications are also warranted regarding the frequency of adverse events of special interest (including any implications for the Defitelio label), deaths, graft failures and laboratory findings.

8. PRAC advice

At the meeting of PRAC held 2 – 5 May 2022, the draft DHPC and communication plan, as provided by the MAH on 28 April, 2022 and further commented by the rapporteurs were discussed by the PRAC.

The PRAC noted the CHMP assessment of study 15-007, which is a study undertaken in a non-approved population, but nevertheless is included in the RMP as a category 3 study. The PRAC also noted the conclusions drawn in the assessment report; that the main efficacy results from this study, together with the already well-established safety profile of defibrotide, further support that the benefit/risk balance for the use of defibrotide as prophylaxis for VOD after HSCT is negative.

The PRAC also noted results from other procedures, such as variations II-48 and II-58, which point to relatively extensive off label use of defibrotide as prophylaxis for VOD after HSCT.

Given the well-established safety profile, the lack of benefit as shown in study 15-007, and the documented off label use as prophylaxis for VOD after HSCT, the PRAC agrees with the CHMP that there is a need to clearly communicate this to health care professionals. The PRAC also finds is appropriate that health care professionals are advised not to use defibrotide as prophylaxis for VOD after HSCT, to protect such patients from harm without potential benefits of the exposure. Therefore, a revised DHPC is proposed, as available in an Annex. A revised draft communication plan is also provided.

9. Risk management plan

The MAH submitted an updated RMP version with this application. The (main) proposed RMP changes were the following:

Removal of Study 15 007 from part III (Pharmacovigilance plan) and part V (Risk minimisation measures)

Pharmacovigilance plan

(…)

III.2 Additional Pharmacovigilance Activities

~~**Study 15-007 summary**~~

~~Study short name and title: Study 15-007; randomized, adaptive study comparing the efficacy and safety of defibrotide vs best supportive care in the prevention of hepatic VOD in adult and pediatric patients undergoing HSCT~~

~~Rationale and study objectives: To obtain comparative safety data~~

~~Study design: Open label, randomized, adaptive~~

~~Study population: Adult and paediatric patients undergoing HSCT who are at a high risk or very high risk of developing VOD~~

~~Milestones: Final report by end of June 2021~~

DEFIFrance

Study short name and title: DEFIFrance; A National, Post-Registration, Observational Study of the Long-term Safety and Health Outcome of Patients Treated With Defitelio, Including Patients With Severe Hepatic VOD After HSCT.

Rationale and study objectives: To investigate the safety and outcome of patients treated with defibrotide in France from 15 Jul 2014 (labelled indication as well as off-label use)

Study design: Multi-center, national, observational retrospective and prospective study

Study population: All patients treated with defibrotide from 15 July 2014

Milestones: Q4 2021

III.3 Summary Table of Additional Pharmacovigilance Activities

Study **Status**	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None	Not applicable	Not applicable	Not applicable	
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None ~~Study 15-007 A Phase 3, randomized, adaptive study comparing the efficacy and safety of defibrotide vs. Best Supportive Care in the prevention of hepatic VOD in patients undergoing HSCT.~~ ~~Ongoing~~	~~To obtain comparative safety data~~	~~All known and potential risks and data for missing information~~	~~Final report (Planned)~~	~~End of June 2021~~
Category 3 - Required additional pharmacovigilance activities				
DEFIFrance A National, Post-Registration, Observational Study of the Long-term Safety and Health Outcome of Patients Treated With Defitelio®, Including Patients With Severe Hepatic VOD After HSCT. **Ongoing**	To investigate the safety and outcome of patients treated with defibrotide in France from 15 Jul 2014 (labelled indication as well as off-label use)	All known and potential risks and data for missing information	Final report (Planned)	Q4 2021

Risk minimisation measures

(…)

V.3 Summary of Risk Minimization Measures

Study 15-007 has been removed as an additional pharmacovigilance activity for the following safety concerns: Haemorrhage, Hypotension, Coagulopathy, Immunogenicity, Thromboembolic events, Patients treated concomitantly with defibrotide and medications that increase the risk of haemorrhage (including the newer oral anti-coagulants direct thrombin and factor Xa inhibitors), Patients with pre-existing liver or severe renal insufficiency (aetiologies other than VOD) and Patients with intrinsic lung disease.

Elements for a public summary of the RMP

(…)

II.B Summary of Important Risks

Study 15-007 has been removed as additional pharmacovigilance activity for the safety concerns as stated above.

Annexes

Annex 2 has been updated to move study 15-007 from ongoing to completed studies.

Assessor's comment:

Study 15-007 has been completed. Formally, removal of this study from the RMP could be accepted; however, there are several outstanding issues regarding the safety concerns (for which this study was one additional PhV activity) that warrant clarification within this procedure before the proposed RMP updates could be approvable. This includes haemorrhage, hypotension, coagulopathy, thromboembolic events, immunogenicity, concomitant treatments and patients with pre-existing liver disease/renal insufficiency/intrinsic lung disease. (**LoQ**)

9.1. Overall conclusion on the RMP

☒The changes to the RMP and the changes to the conditions and obligations of MA could be acceptable provided satisfactory responses to the request for supplementary information are submitted.

10. Changes to the Product Information

As a result of this variation, the MAH proposes only to remove study 15-007 from the Opinion Annex II conditions as detailed in the recommendations section above.

However, since previous prophylactic studies have been included in the SmPC and since study 15-007 also includes study data on treatment with defibrotide for VOD, the SmPC sections 4.8 and 5.1 should be updated to include data from study 15-007.

Additional amendments of the SmPC will depend on the responses to the RSI.

The Package Leaflet (PL) should be updated accordingly.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

11. Request for supplementary information

11.1. Major objections

Clinical aspects

Safety

1. There was a numerical imbalance in favour of best supportive care for VOD-free survival both during the prophylaxis period of study 15-007 and more pronounced during the rescue treatment period. These data are in line with previous prophylaxis data indicating increased mortality with defibrotide treatment, especially in the paediatric population. These data may question the safety of defibrotide also in the approved indication considering that the populations studied in the prophylaxis studies are similar to the population covered by the approved indication. To further address the safety profile and in particular the apparent imbalance in mortality with defibrotide treatment, and to address this issue in relation to the approved indication, the MAH should:

    a. clarify the number of events of VOD and deaths respectively in study 15-007 that contributed to the primary efficacy endpoint for the entire study population and divided by age groups (paediatric subjects vs adults)

    b. present the 'other reasons' for censoring in the presentation of the primary efficacy outcome events in more detail, including any imbalance between treatment groups

    c. provide the total number of deaths up to day 30-post-HSCT in study 15-007 divided by age groups (paediatric subjects vs adults) including causes of death.

    d. provide survival data separated by subjects diagnosed with VOD during study 15-007 who received defibrotide and those diagnosed with VOD who did not receive defibrotide

    e. clarify the severity of VOD in those who received VOD for rescue treatment, and provide survival data for severe VOD for the entire study population and divided by age groups (paediatric subjects vs adults)

    f. discuss the above findings in relation to the totality of data on survival in subjects treated with defibrotide, both in prophylaxis studies and VOD-treatment studies, with a separate discussion on paediatric patients

11.2. Other concerns

Clinical aspects

Efficacy

2. A clarification is warranted on the apparently discrepant number of subjects with VOD recognised by investigators and subjects who actually received defibrotide for VOD rescue treatment in study 15-007.
3. The MAH should discuss the vast difference between investigators and EPAC assessments of VOD and date of VOD diagnosis in more detail, including the diagnostic criteria used and their clinical relevance.
4. The MAH should present the data on VOD-resolution in subjects diagnosed with VOD (including severity assessment) during study 15-007, divided by those who received defibrotide and those diagnosed vid VOD who did not receive defibrotide, for the entire study population and divided by age groups (paediatric subjects vs adults).
5. One third of the ITT population in study 15-007 had major protocol deviations, primarily related to study "procedures/assessments". The MAH should provide the most frequent reasons for deviation in study procedures/assessments and discuss the integrity of the study given the large number of major protocol deviations.

Safety

6. The MAH should clarify whether subjects treated concomitantly with defibrotide and medications that increase the risk of haemorrhage were adequately captured in study 15-007, and provide outcome data in terms of VOD, bleeding events and TEAEs for these subjects.
7. A summary of the TEAEs and the treatment-related TEAEs in study 15-007 should be provided, separated by children and adults using the number of children and adults respectively as the denominator when presenting percentages. Any differences between treatment groups as well as any differences between age groups should be addressed, including any implications for the labelling of adverse reactions.
8. The MAH is asked to clarify why only 10 of the deaths that occurred in each treatment arm during the "prophylaxis phase" of study 15-007 were included in the presentation of TEAE leading to death up to day +180 post-HSCT; even when adding those who were diagnosed with VOD and died due to adverse events, the figures are not congruent with the overall presentation of death during the study.
9. For all three adverse events of special interest (pulmonary, haemorrhage, gastrointestinal haemorrhage, hypersensitivity) which are also labelled adverse reactions for Defitelio, the reported event rates during rescue treatment appear higher than what would be expected based on the current label. The MAH should discuss these data in relation to the labelled frequencies and propose any label updates if warranted.
10. Immunogenicity was an exploratory endpoint for which no data have been provided. However, this is one of the safety concerns addressed by this study. Considering also the difference in hypersensitivity reactions between prophylaxis treatment arms in subjects who developed VOD and were treated with defibrotide, the MAH should provide the immunogenicity data.

11. A summary of all vital sign variables recorded should be presented for the respective treatment group at baseline and at day 30 post-HSCT for the prophylaxis period, and at diagnosis of VOD and at day +30 post-VOD treatment for the rescue treatment period. These data should be provided for the overall study population (safety analysis set) and divided by age groups (paediatric subjects vs adults).

12. During the rescue phase, 4 participants (16.0%) in the DP arm and 3 participants (9.7%) in the BSC arm experienced graft failure. The MAH is asked to discuss these findings on graft failure during the rescue phase in more detail, including any possible relation to defibrotide.

13. For abdominal ultrasound results, no summary of data has been provided; the MAH is asked to provide a summary of the findings in each treatment group, for the overall study population (safety analysis set) and divided by age groups (paediatric subjects vs adults).

14. A summary of the variables recorded for the laboratory findings should be presented for the respective treatment group at baseline and at day 30 post-HSCT for the prophylaxis period, and at diagnosis of VOD and at day +30 post-VOD treatment for the rescue treatment period. These data should be provided for the overall study population (safety analysis set) and divided by age groups (paediatric subjects vs adults).

15. For the additional safety concerns addressed by this study that are not covered by the above RSI, a summary of the main clinical findings should be presented. This pertains to thromboembolic events, patients with pre-existing liver disease, patients with pre-existing renal insufficiency and patients with intrinsic lung disease. Data should be presented for the respective treatment group at baseline and at day 30 post-HSCT for the prophylaxis period, and at diagnosis of VOD and at day +30 post-VOD treatment for the rescue treatment period, and should be provided for the overall study population (safety analysis set) and divided by age groups (paediatric subjects vs adults).

SmPC

16. Since previous prophylactic studies have been included in the SmPC and since study 15-007 also includes study data on treatment with defibrotide for VOD as well as paediatric data, the SmPC sections 4.8 and 5.1 should be updated to include data from study 15-007.

12. Assessment of the responses to the request for supplementary information

12.1. Major objections

Clinical aspects

Safety

Question 1. *There was a numerical imbalance in favour of best supportive care for VOD-free survival both during the prophylaxis period of study 15-007 and more pronounced during the rescue treatment period. These data are in line with previous prophylaxis data indicating increased mortality with defibrotide treatment, especially in the paediatric population. These data may question the safety of defibrotide also in the approved indication considering that the populations studied in the prophylaxis studies are similar to the population covered by the approved indication. To further address the safety profile and in particular the apparent imbalance in mortality with defibrotide treatment, and to address this issue in relation to the approved indication, the MAH should:*

a. clarify the number of events of VOD and deaths respectively in study 15-007 that contributed to the primary efficacy endpoint for the entire study population and divided by age groups (paediatric subjects vs adults)

b. present the 'other reasons' for censoring in the presentation of the primary efficacy outcome events in more detail, including any imbalance between treatment groups

c. provide the total number of deaths up to day 30-post-HSCT in study 15-007 divided by age groups (paediatric subjects vs adults) including causes of death.

d. provide survival data separated by subjects diagnosed with VOD during study 15-007 who received defibrotide and those diagnosed with VOD who did not receive defibrotide

e. clarify the severity of VOD in those who received VOD for rescue treatment, and provide survival data for severe VOD for the entire study population and divided by age groups (paediatric subjects vs adults)

f. discuss the above findings in relation to the totality of data on survival in subjects treated with defibrotide, both in prophylaxis studies and VOD-treatment studies, with a separate discussion on paediatric patients

Summary of the MAH's response

1a. clarify the number of events of VOD and deaths respectively in study 15-007 that contributed to the primary efficacy endpoint for the entire study population and divided by age groups (paediatric subjects vs adults)

The primary efficacy endpoint of Study 15-007 was veno-occlusive disease (VOD)-free survival at Day +30 post-hematopoietic stem cell transplant (HSCT) as per the independent Endpoint Adjudication Committee (EPAC). Note that the EPAC charter on evaluation of VOD was included as an appendix to the Study 15-007 clinical study report (CSR) submitted April 2021: Module 5.3.5.4/JZP15-007 CSR/Section 8.9.7. An event for the primary efficacy endpoint was defined as a VOD diagnosis (as assessed by the EPAC) or death from any cause, whichever occurred earlier, up to and including Day +30 post-HSCT.

Overall, of 372 total participants included in the study, 90 were evaluable for the primary endpoint. Fifty participants (pediatric n=32, adults n=18) in the defibrotide prophylaxis (DP) arm and 40

participants (pediatric n=20, adult n=20) in the best supportive care (BSC) arm contributed to the primary efficacy endpoint.

Of the 90 participants, the majority of events were VOD (DP arm 94.0%; BSC arm 95.0%) and the rest were Death without VOD (DP arm n=3, BSC arm n=2). No substantial difference was observed between the treatment arms in the event rates that contributed to the primary endpoint overall or by age group.

Table 18. Primary Efficacy Endpoint: VOD-free Survival by Day +30 post-HSCT - Summary of the Events of Interest (ITT Analysis Set)

Age Group Variable, Statistic	DP (N=190)	BSC (N=182)
Overall		
Number of Subjects, n (%)	50	40
VOD	47 (94.0)	38 (95.0)
Death without VOD	3 (6.0)	2 (5.0)
Pediatric Subjects (<=16 years)		
Number of Subjects, n (%)	32	20
VOD	31 (96.9)	18 (90.0)
Death without VOD	1 (3.1)	2 (10.0)
Adult Subjects (>16 years)		
Number of Subjects, n (%)	18	20
VOD	16 (88.9)	20 (100.0)
Death without VOD	2 (11.1)	0 (0.0)

BSC = Best Supportive Care; DP = Defibrotide Prophylaxis; ITT = intent-to- treat; VOD = Veno-Occlusive Disease n = the number of subjects who experienced any event of interest by Day +30 post-HSCT within each treatment arm in the specified age group from the ITT Analysis Set. Percentages were calculated with n as a denominator.

Assessment of the MAH's response

The MAH has clarified the number of deaths respectively that contributed to the composite primary efficacy outcome of VOD-free Survival by Day +30 post-HSCT. Of the 50 primary efficacy outcome events in the defibrotide group, 47 were VOD and 3 were deaths without VOD. The majority of events (N = 32) in the defibrotide group occurred among paediatric subjects (</=16 years of age); 31 of these were VOD and 1 was death without VOD. For best supportive care, there were 40 events; 38 were VOD and 2 were deaths without VOD with a similar number of events among paediatric subjects as in adults (20 event each).

Conclusion

Issue resolved.

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

1b. present the 'other reasons' for censoring in the presentation of the primary efficacy outcome events in more detail, including any imbalance between treatment groups

The majority of participants who were censored in either the defibrotide prophylaxis (DP) arm (84.3%) and the best supportive care (BSC) arm (83.1%) were censored for having "No VOD or No Death by Day +30 post-HSCT".

The primary efficacy endpoint of Study 15-007 was veno-occlusive disease (VOD)-free survival at Day +30 post-hematopoietic stem cell transplant (HSCT) as adjudicated by the independent Endpoint Adjudication Committee (EPAC). An event for the primary efficacy endpoint was defined as a VOD diagnosis (as assessed by the EPAC) or death from any cause, whichever is earlier, up to and including Day +30 post-HSCT. VOD diagnosis by EPAC had the following options: VOD Yes/No; Not applicable (no HSCT), or Not evaluable. The adjudication process and adjudication criteria are described in the EPAC charter (Module 5.3.5.4/JZP15-007 CSR/Section 8.9.7). Analysis of the primary endpoint, including reasons for censoring, is described in the Statistical Analysis Plan (SAP; Module 5.3.5.4/JZP15-007 CSR/CSR Section 8.8.6/SAP Section 10.1).

A total of 140 participants (73.7%) in the DP arm and 142 participants (78.0%) in the BSC arm were censored in the primary efficacy endpoint analysis Module 5.3.5.4/JZP15-007 CSR/Table 14.2.1.1).

Table **19** below summarizes number and percent of participants in each treatment arm who were censored in the primary efficacy endpoint analysis and the reason for censoring. Censoring rules and rationale are pre-specified in the Statistical analysis Plan (SAP), Section 10.1. A higher percentage of participants in the DP arm compared to the BSC arm were censored because they were not evaluable by Day +30 post-HSCT (DP arm 6.4%; BSC arm 2.8%) or because the participant did not undergo HSCT (DP arm 7.9%; BSC arm 5.6%). Eleven (7.7%) participants in the BSC arm received defibrotide as rescue treatment but were not diagnosed with VOD by EPAC and were, therefore, censored for the primary endpoint analysis at the date of rescue treatment initiation. Further details of difference between EPAC and investigator assessment of VOD are described in response to Question 3. A small number (DP arm n=2, BSC arm n=1) were censored due to having VOD or dying prior to HSCT.

Table 19. Primary Efficacy Endpoint: VOD-free Survival by Day +30 post-HSCT – Summary of Censoring Events (ITT Analysis Set)

Variable, Statistic	**DP N=190**	**BSC N=182**
Number of Subjects, n (%)		
Censored	140	142
No VOD/Death by Day +30 post-HSCT	118 (84.3)	118 (83.1)
Not Evaluable by Day +30 post-HSCT	9 (6.4)	4 (2.8)
Event occurred prior to HSCT	2 (1.4)	1 (0.7)
Subject did not undergo HSCT	**11 (7.9)**	**8 (5.6)**
Rescue Treatment	**0 (0.0)**	**11 (7.7)**

Abbreviations: BSC = Best Supportive Care; DP = Defibrotide Prophylaxis; HSCT = hematopoietic stem cell transplant; ITT = intent-to-treat; VOD = Veno-Occlusive Disease n = the number of censored subjects within each treatment arm from the ITT Analysis Set Percentages were calculated with n as a denominator. The category of Rescue Treatment includes subjects in the BSC arm who received rescue treatment with Defibrotide but VOD was not confirmed by EPAC. These subjects were censored at the date of rescue initiation.

Assessment of the MAH's response
The MAH has clarified the 'other reasons' for censoring. It is noted that in the table above, individuals without VOD (based on EPAC assessment) but were considered to have VOD by investigators and received rescue treatment with defibrotide are separated from the group 'no VOD/death'; this is not considered appropriate as the assessment of VOD for the primary efficacy outcome events was solely based on the blinded EPAC assessment.

There were more subjects who were not evaluable by Day +30 post-HSCT in the defibrotide group (6.4%) as compared to best supportive care (2.8%); further, there were more participants in the defibrotide group that did not undergo HSCT (7.9%) as compared to best supportive care (5.6%). Thus, at Day +30 post-HSCT include fewer evaluable subjects who had actually undergone HSCT in the defibrotide group as compared to best supportive care.

Conclusion

Issue resolved*;* see also below for discussion on diagnosis of VOD by EPAC vs investigators.

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

1c. provide the total number of deaths up to day 30-post-HSCT in study 15-007 divided by age groups (paediatric subjects vs adults) including causes of death.

Listing 16.2.21 presents all deaths by Day +30 post-HSCT for each age subgroup (pediatric participants [≤ 16 years old] and adult participants [> 16 years]) by treatment arm and includes participant ID and relevant demographics, date of HSCT, date of death, and primary cause of death (as captured on the death electronic case report form [eCRF]), and any Grade 5 adverse event (AE), if reported on the AE eCRF. A participant could have had more than one Grade 5 AE recorded, and all are listed.

Through Day +30 post-HSCT, a total of 15 participants died (defibrotide arm [DP] arm n=10 [5.7%]; Best Supportive Care [BSC] arm, n=5 [2.9%]). Of these 15 participants, 6 were pediatric participants (DP arm n=4; BSC arm, n=2), and 9 were adult participants (DP arm n=6; BSC arm, n=3). None of the causes of death were assessed by the investigator as related to defibrotide treatment. Further details regarding the 6 pediatric participants included in this analysis who died (DP arm n=4; BSC arm, n=2) by Day +30 post-HSCT are as follows:

- DP arm: 1 participant died due to Candida sepsis and multiple organ dysfunction (MOD) syndrome; 1 participant cause of death included Haemorrhage intracranial, 1 participant died from Histiocytosis haematophagic, and 1 participant due to Pseudomonal sepsis.
- BSC arm: 1 participant died due to Respiratory failure and 1 from Pulmonary haemorrhage.

No pediatric participant died from VOD in either arm of the study by Day +30 post HSCT.

A total of 9 adult participants died (DP arm n=6; BSC arm, n=3) by Day +30 post-HSCT. Further details regarding cause of death for adult participants are as follows:

- DP Arm: causes of death included MOD syndrome with VOD (n=1), VOD (n=1), Posterior reversible encephalopathy syndrome (n=1), Septic shock (n=1), Acute myeloid leukaemia recurrent (n=1), and 1 participant had 3 AEs reported as Grade 5/fatal (Acute kidney injury, Bronchopulmonary aspergillosis, and VOD). For this last participant (Participant ID 8205-1001), the coded Preferred Term (PT) of VOD was captured as a cause of death (Listing 16.2.21), yet the AE verbatim term was

reported as "early VOD" (Module 5.3.5.4/JZP15-007 CSR/Listing 16.2.10.5). On Day +8 post-HSCT, the participant experienced Bronchopulmonary aspergillosis and Acute kidney injury, and on the same day, the participant was diagnosed with VOD-associated MOD (Module 5.3.5.4/JZP15-007 CSR/Listing 16.2.8.2). On Day +18 post-HSCT, the participant experienced Grade 5 serious adverse events of Venooclusive disease, worsening of Bronchopulmonary aspergillosis, and Acute kidney injury.

- BSC Arm: Causes of death for the 3 adult participants in the BSC included MOD syndrome with VOD, Pneumonia, and Sepsis (n=1 each). Of the Grade 5 AEs, none were assessed by the investigator as related to defibrotide treatment (Module 5.3.5.4/JZP15-007 CSR/Listing 16.2.10.5).

Individual participant narratives describing all deaths (through Day +180 post-HSCT) are provided in Module 5.3.5.4/JZP15-007 CSR/Section 11.

The MAH would like to clarify that the total number of deaths by Day +30 post-HSCT in this analysis (pediatric n=6, adult n=9) appears different from the total number of deaths (pediatric n=3, adult n=2) presented in response to Question 1a. The reason for this is that, per the protocol and statistical analysis plan, the definition of an event that contributed to the primary endpoint was VOD or death from any cause, whichever is earlier, up to and including Day +30 post- HSCT (response to Question 1a). Therefore, only deaths that occurred first (DP arm n=3, BSC arm n=2) contributed to the primary endpoint, while all deaths (including the 5 deaths that contributed to the primary endpoint) from any cause in all participants that occurred by Day +30 post HSCT are included in this response.

In summary the number of deaths, overall and by age group, were comparable between the 2 treatment arms in the study. Our data are consistent with what has been published in the literature regarding the main causes of mortality post-HSCT (particularly allogeneic) being primary disease relapse, early treatment-related mortality, including infections, toxicity, and graft-vs-host disease (Styczyński 2020). The participants who died by Day +30 post-HSCT in this study had causes of death that were primarily due to transplant-associated adverse events and are consistent with reported evidence on early mortality post-HSCT.

Reference: Styczyński J, Tridello G, Koster L et al,. Death after hematopoietic stem cell transplantation: changes over calendar year time, infections and associated factors. BMT (2020) 55:126–136.

Assessment of the MAH's response

There were 10 deaths up to day 30-post-HSCT in the defibrotide group and 5 in the best supportive care group. Of these, 6 were paediatric participants (defibrotide group, n=4; best supportive care group, n=2), and 9 were adult participants (defibrotide group n=6; best supportive care group, n=3).

It is stated that no paediatric participant died from VOD in either arm of the study by Day +30 post HSCT; however, at least one child died due to multiple organ dysfunction syndrome in the defibrotide group during this period. Further, one child died due to intracranial haemorrhage (which is a labelled adverse event for defibrotide).

Apparently, given the difference between total number of deaths and deaths contributing to the primary efficacy outcome, there majority of deaths occurred in subjects who were first diagnosed with VOD and then died (7 subjects in the defibrotide group and 3 subjects in the best supportive care group).

Conclusion

Issue partly resolved*; further discussion on mortality requested.*

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

1d. provide survival data separated by subjects diagnosed with VOD during study 15-007 who received defibrotide and those diagnosed with VOD who did not receive defibrotide

The MAH would like to highlight that survival analysis, as requested by the Agency, separated by participants diagnosed with VOD during Study 15-007 who received defibrotide and those diagnosed with VOD who did not receive defibrotide, is not feasible nor a valid comparison. The reason is described as follows:

Per study 15-007 protocol, the analysis was based on the blinded Endpoint Adjudication Committee (EPAC) assessment of VOD. EPAC assessment of VOD was done retrospectively based on electronic forms, and it did not influence the decision regarding participants receiving defibrotide rescue treatment, which was made by the Principal Investigator (PI). Defibrotide rescue treatment was administered to participants only based on clinical assessment and diagnoses of VOD by the PI. All participants who were diagnosed with VOD based on PI assessment (n=57) received defibrotide rescue treatment, except for 1 participant who was withdrawn from the study before receiving defibrotide rescue treatment.

A total of 96 participants were diagnosed with VOD by EPAC:

- Of these 96 participants, 38 were also diagnosed with VOD by the PI (100% concordance, Question 3) and received defibrotide rescue treatment. This group (n=38) represents those with VOD who received defibrotide rescue treatment.

- The remaining 58 participants (n=96-38) who were diagnosed with VOD by EPAC but who were not diagnosed by the PI and did not receive defibrotide rescue treatment. These participants most likely did not experience clinical VOD warranting treatment.

This clinical study was designed to test the potential for defibrotide prophylaxis (DP) to prevent VOD and included a provision for participants with a VOD diagnosis according to the PI to receive rescue therapy with defibrotide (25 mg/kg/day) in either the DP and BSC arms of the study. It was not designed to evaluate defibrotide in the treatment of VOD. The study was not randomized at the rescue phase for those participants who developed VOD; therefore, based on EPAC retrospective assessment of VOD, 2 different groups resulted 1) a VOD group (diagnosed by both EPAC and PI) and treated with rescue defibrotide and 2) a group with VOD diagnosis only (by EPAC) who did not receive defibrotide rescue treatment. The latter group likely did not experience clinical VOD, hence, cannot be considered "VOD who did not received defibrotide treatment" but rather, "no VOD who did not receive defibrotide rescue treatment". Therefore, a treatment comparison is not valid. As evidenced from the literature, patients diagnosed with VOD have a much poorer prognosis than patients not diagnosed with VOD (Coppell 2010).

References

Coppell JA, Richardson PG, Soiffer R, et al. Hepatic veno-occlusive disease following stem cell transplantation: incidence, clinical course, and outcome. Biol Blood Marrow Transplant 2010;16(2):157-68.

Assessment of the MAH's response

The MAH argumentation that EPAC adjudicated VOD was not actually VOD cannot be followed. Based on this argumentation, the entire study design would be questioned as VOD adjudicated by the EPAC formed the basis for the primary efficacy outcome assessment. The very strength of this study is the blinded external adjudication committee. This is also a strength that appears unique for this defibrotide

study since previous defibrotide studies have not had any blinded assessments. There is a clear discordance between VOD as assessed by investigators and VOD as assessed by a blinded external committee. The discordance was most pronounced among subjects who received defibrotide, which could implicate a potential bias among the open-label investigators.

According to the protocol, it is understood that both investigators and the EPAC were to apply modified Seattle criteria for the assessment/diagnosis of VOD. All data of interest was provided to the EPAC as outlined in Q3 below. There is no data or discussion on e.g., potential differences in severity of VOD that could have affected the outcome (see also assessment of Q3 below).

This question is of clear interest to assess the safety profile of defibrotide also for the approved indication and the requested data should be provided.

Conclusion

Issue not resolved. The requested data should be provided.

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

1e. clarify the severity of VOD in those who received VOD for rescue treatment, and provide survival data for severe VOD for the entire study population and divided by age groups (paediatric subjects vs adults)

The MAH would like to clarify that in the Agency request above, the phrase "…who received VOD for rescue treatment, …" is interpreted by the MAH to indicate "…who received defibrotide for rescue treatment…"

A total of 56 subjects received rescue treatment, 30/56 (54%) were pediatric and 26/56 (46%) were adult participants. (Module 5.3.5.4/JZP15-007 CSR/Table 14.1.2.3). Veno-occlusive disease (VOD) was not classified by severity in the Study 15-0007; therefore, we are providing data on VOD cases with Multiple organ dysfunction (MOD). Of those with VOD, 19/56 (34%) (pediatrics n=10, adult n=9) had VOD with MOD (Module 5.3.5.4/JZP15- 007/Table 14.2.2.5 and Listing 16.2.8.2). The remaining, 37/56 (66%) (pediatric n=20, adult n=17) had VOD with no MOD.

Per Study 15-007 protocol, the primary endpoint analysis was based on the blinded Endpoint Adjudication Committee (EPAC) assessment of VOD; however, the severity of VOD was not defined per protocol nor per EPAC charter. Participants with severe VOD could only be identified if they had concomitant VOD-associated MOD reported based on investigator assessment.

A total of 19 participants (pediatric n=9 and adult n=10) who were diagnosed with VOD by the Principal Investigator (PI), and had a VOD associated MOD reported in eCRF, were also diagnosed with VOD by EPAC (100% concordance). These 19 participants were the total number of participants in the study population (n=372) who had reported VOD associated MOD, and as such can be considered as severe VOD (VOD with MOD) and all received rescue treatment with defibrotide. The 19 participants with VOD with MOD comprised 20% (n=19/96) and 33% (n=19/57) of the total participants diagnosed with VOD by the EPAC and PI, respectively.

<u>Survival in participants with VOD with MOD for the entire study population and divided by age group</u>

A survival analysis for participants with severe VOD who received defibrotide rescue treatment is provided in Table 20 below by treatment arm and by pediatric or adult. The analysis was performed from the date of VOD diagnoses for each participant. Of the 19 participants who were diagnosed with

severe VOD described above, 18 participants were included in this analysis. One participant was excluded due to the date of VOD diagnosis by EPAC after completion of defibrotide rescue treatment, which was initiated by the PI.

Overall, 9 of the 18 (50%) participants with VOD with MOD died. For the overall population with VOD with MOD, the Kaplan-Meier (KM) estimate of median survival time in days was 99.0 (95% confidence interval [CI] 25.0, not estimable [NE]). In pediatric participants, 4/10 (40%) died with a KM estimate of median survival time in days of 146.0 (95% CI 12.0, NE). In adult participants, 5/8 (62.5%) died with a KM estimate of median survival time in days of 47.0 (95% CI 9.0, NE). In summary, the estimated proportion of participants who were diagnosed with VOD with MOD (19 to 33%) is in line with evidence from published literature (Coppell 2010).

Table 20 Overall Survival after Diagnosis of VOD with MOD based on EPAC Assessment (ITT Analysis Set)

Subjects Diagnosed with VOD with MOD			
Age Group Variable, Statistic	DP Arm	BSC Arm	Overall
Overall			
Number of Subjects, n(%)	9	9	18
Death	5 (55.6)	4 (44.4)	9 (50.0)
Censored	4 (44.4)	5 (55.6)	9 (50.0)
KM Estimate of Median Survival Time in Days (95% CI)	65.5 (12.0, NE)	146.0 (9.0, NE)	99.0 (25.0, NE)
Pediatric Subjects(<=16 years)			
Number of Subjects, n(%)	5	5	10
Death	2 (40.0)	2 (40.0)	4 (40.0)
Censored	3 (60.0)	3 (60.0)	6 (60.0)
KM Estimate of Median Survival Time in Days (95% CI)	62.0 (12.0, NE)	146.0 (99.0, NE)	146.0 (12.0, NE)
Adult Subjects(>16 years)			
Number of Subjects, n(%)	4	4	8
Death	3 (75.0)	2 (50.0)	5 (62.5)
Censored	1 (25.0)	2 (50.0)	3 (37.5)
KM Estimate of Median Survival Time in Days (95% CI)	40.5 (12.0, NE)	NE	47.0 (9.0, NE)

Abbreviations: BSC = Best Supportive Care; CI = confidence interval; DP = Defibrotide Prophylaxis;; KM = Kaplan-Meier; MOD = Multi-Organ Dysfunction; NE = not estimable; VOD = Veno-Occlusive Disease; n = the number of subjects diagnosed with VOD with MOD in the specified age group. Percentages were calculated with n as a denominator. Survival time = [Date of death] Source: Table 14.2.7.1

References: Coppell JA, Richardson PG, Soiffer R, et al. Hepatic veno-occlusive disease following stem cell transplantation: incidence, clinical course, and outcome. Biol Blood Marrow Transplant 2010;16(2):157-68.

Assessment of the MAH's response

The majority of subjects who received defibrotide for treatment of VOD had no multi-organ dysfunction/failure. When defibrotide was approved, severe VOD was defined as VOD with MOD/MOF. Since then, the terminology has changed, see also introduction; **severe VOD in adults** is diagnosed according to the following (Mohty et al 2016; at least two criteria are required): time since first clinical symptoms of VOD =/< 4 days, bilirubin (µmol/L) between 85 and 136, bilirubin levels doubling within 48 h, transaminases more than 5 and less than 8 x UNL, weight increase between 5 and 10% and renal function impaired by more than a factor 1,5 and less than 2 as compared to at transplant. Of note, with these criteria, patients are not required to have multi-organ dysfunction/failure to be classified as 'severe' – if multi-organ failure is present, the patient is classified as very severe VOD. For **severe VOD in paediatric patients**, the following criteria are included: liver function tests > 5 x ULN, persistent refractory thrombocytopenia > 7 days, bilirubin (µmol/L) >34, ascites with necessity for paracentesis, impaired coagulation and impaired renal function with GRF (mL/min) 29-15, need for invasive pulmonary ventilation and normal CNS function (Corbacioglu 2018). Also for paediatric patients, if MOD/MOF is present, the severity is graded as 'very severe'.

Based on the protocol, it would likely be possible to assess the severity of VOD in those who received defibrotide for rescue treatment during the initial +30 days post-HSCT, since extensive clinical laboratory testing including parameters of interest were scheduled for daily sampling during hospitalization, as were weight, physical examination/vital signs and hospitalization data. Assessments of VOD and VOD-associated MOD were scheduled twice weekly during the initial +30 days and weekly up to day +60. Although it is recognized that the terminology was changed at the same time that this study was initiated (or during the study for paediatric patients), an attempt to discuss the outcomes in patients treated with defibrotide based on severity of VOD would have been appreciated to this aid in assessing outcomes based on the current label and thus the appropriateness of the current label. However, the MAH states that the severity of VOD was not defined per protocol nor per EPAC charter. The Table 20 above is thus interpreted to actually be participants with VOD as per EPAC that had MOF as per investigators' assessments.

The presented data on survival in subjects with VOD with multiorgan dysfunction are thus representing patients with 'very severe VOD' based on current terminology. All these subjects received defibrotide for rescue treatment. The grouping into defibrotide arm and best supportive care is based on the initial randomization. It is found worrisome that initial randomization to defibrotide was apparently associated with a shorter median survival time in subjects who developed VOD with MOD and who were treated with defibrotide.

Conclusion

Issue partly resolved; *further discussion on mortality requested.*

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

1f. discuss the above findings in relation to the totality of data on survival in subjects treated with defibrotide, both in prophylaxis studies and VOD-treatment studies, with a separate discussion on paediatric patients

Study 15-007 was an adaptive design Phase 3 clinical study (15-007) comparing the efficacy and safety of defibrotide prophylaxis (DP) versus best supportive care (BSC) in the prevention of hepatic veno-occlusive disease (VOD) in adult and pediatric patients undergoing hematopoietic stem cell transplant (HSCT) who are at high risk or at very high risk of developing VOD. Study 15-007 was a Post- Marketing Requirement (PMR)/ Specific Obligation to collect additional data to support the safety of defibrotide in a randomized multicenter clinical trial. The prevention Study 15-007 was used for this PMR due to ethical limitations in performing randomized studies in the treatment of VOD, a critical condition with a mortality of > 80% if left untreated, and to collect such safety data given the availability and the established efficacy of defibrotide as a valid treatment option.

Prior data suggested that defibrotide could be effective in preventing VOD. Several studies have previously shown the benefit of defibrotide in prophylaxis of VOD vs standard of care (Corbacioglu 2012, Chalandon 2004, Zhang 2004). In addition, a more recent pooled analysis was conducted using 19 studies totaling 2929 participants that evaluated intravenous (IV) defibrotide for VOD/SOS prophylaxis (Corbacioglu 2021). In this metanalysis, the overall VOD/SOS incidence with IV defibrotide was 5%, (5% incidence of VOD in adults and 8% in pediatric patients). In 8 studies evaluating IV defibrotide prophylaxis versus controls (eg, heparin, no prophylaxis), VOD/SOS incidence in controls was 16%. The risk ratio for developing VOD/SOS with defibrotide prophylaxis versus controls was 0.30 (95% confidence interval [CI] 0.12, 0.71; p=0·0002). The current study 15-007 was based on the earlier evidence, albeit with confounding factors in the study design, discussed herein, which need to be taken into consideration in interpreting the results and comparison to earlier studies in defibrotide prevention of VOD.

In April 2020, new enrolment into the study was stopped due to futility. The decision for early stopping was based on a recommendation from an independent Data Monitoring Committee (DMC) after a pre-planned interim analysis on the first 280 patients randomized in the study. The DMC concluded that the study was unlikely to meet its primary endpoint should enrollment continue to the total of 400 participants originally planned or increase in size. The DMC conducted multiple periodic safety analyses during the study and reported no new safety concerns, including the point at which the IDMC recommended stopping the trial for futility with respect to the primary endpoint. Defibrotide was well tolerated in this study when given as prophylaxis for patients at high risk/very high risk of developing VOD.

The final analysis of study 15-007, based on a total of 372 randomized participants (pediatric n=198, adults n=174), showed that the safety data between the 2 arms (defibrotide prophylaxis [DP] and best supportive care [BSC]) of the study, were comparable. A comparable percentage of subjects experienced any treatment-emergent adverse events (TEAEs), Serious TEAEs, TEAEs leading to Death and AESIs (AEs of Special Interest). No new adverse reactions were identified, and there were no changes to the frequencies of previously identified adverse reactions in either treatment arm of the study, including pediatric patients. The number of deaths in the study population are comparable between the 2 study treatments arms. The Agency is referred to Question 1c and safety questions. The safety results of the study are consistent with the known safety profile of defibrotide in treatment and also the published literature on defibrotide in prophylaxis.

<u>Design and confounding factors</u>

The efficacy endpoint in Study 15-007, evaluating defibrotide in the prevention of VOD, was added based on evidence from earlier studies (Corbacioglu 2012, Chalandon 2004, Zhang). It is worth highlighting that: Study 15-007 was powered to detect a difference in prevention of VOD with DP vs

BSC; it was not powered nor designed to detect a difference in treatment arms nor evaluate the benefit of defibrotide per se in the treatment of VOD. Study 15-007 had a lower number of paediatric participants (n=198) compared to the earlier paediatric prevention study (n=356) (Corbacioglu 2012), on which our study was based.

In addition, several factors inherent in the design of Study 15-007 limit the potential for post-hoc analyses such as for Question 1d, and also limit the potential for cross- study comparisons to prior studies showing defibrotide benefit in prevention of VOD. Per Study 15-007 protocol, the analysis was based on the blinded Endpoint Adjudication Committee (EPAC) assessment of VOD; however, rescue defibrotide treatment was administered only when VOD was diagnosed by Principal Investigators. EPAC assessment of VOD was done retrospectively, and it did not influence the PI's decision to administer defibrotide treatment in participants who developed VOD during the study. Extensive or detailed data on disease status, details of transplant source and were not appropriately captured nor analyzed. The vast difference between PIs' and EPAC assessments of VOD, as it was also noted by the Agency (Question 3), resulted in 2 different subgroups of participants (VOD treated with defibrotide vs VOD not treated with defibrotide) that are considered not comparable. Participants who were assessed with VOD by EPAC and not by the PI likely did not experience a clinical case of VOD. As such a comparison between those who received and did not receive DP among EPAC designated VOD participants is not appropriate.

At the final analysis, the study primary endpoint of VOD-free survival at Day+30, based on EPAC assessment of VOD, was consistent with the conclusion from the DMC at the interim analysis, ie, VOD-free survival by Day +30 post HSCT was similar in the DP arm compared to BSC (Module 5.3.5.4/JZP15-007/Section 5.1.1.1).

However, it is worth noting that VOD-free survival at Day +30 post HSCT based on PI diagnosis of VOD was numerically higher in the DP arm vs BSC, though not statistically significant (see response to Question 3).

In summary, the study provided additional safety data on defibrotide in a randomized setting, to fulfill the Specific Obligation. The safety results from this study are consistent with the defibrotide safety profile in treatment of VOD and evidence from earlier prevention studies. No comparison on the efficacy in the treatment of VOD can be made.

References

Chalandon Y, Roosnek E, Mermillod B, et al. Prevention of veno-occlusive disease with defibrotide after allogeneic stem cell transplantation. Biol Blood Marrow Transplant 2004; 10(5): 347-54.

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Corbacioglu S, Cesaro S, Faraci M, et al. Defibrotide for prophylaxis of hepatic venoocclusive disease in pediatric haematopoietic stem-cell transplantation: an open-label, phase 3, randomised controlled trial. Lancet 2012; 379(9823): 1301-9.

Zhang L, Wang Y, Huang HE, et al. Defibrotide for the prevention of Heaptic Veno-Occlusive disease after haematopoietic stem cell transplantation. A systematic review. Clin Transplant 2021;26:511-519. doi: 10.1111/j.1399-0012.2012.01604.x

Assessment of the MAH's response
This request was a discussion of the totality of data on survival in subjects treated with defibrotide, both in prophylaxis studies and VOD-treatment studies, with a separate discussion on paediatric patients. No discussion on survival has been provided, only a statement that 'the number of deaths in the study population are comparable between the 2 study treatments arms' which appears incorrect as there were twice as many deaths in the defibrotide arm as in the best supportive care arm, see Q1c.

The SOB pertaining to this study explicitly points out that comparative safety data are expected from this study; since these data indicate a higher mortality in participants treated with defibrotide, the mortality data from this study should be discussed in relation to previous data on survival both in prophylaxis studies and VOD-treatment studies, with a separate discussion on paediatric patients.

Conclusion

Issue not resolved. *The requested discussion should be provided.*

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

12.2. Other concerns

Clinical aspects

Efficacy

Question 2 *A clarification is warranted on the apparently discrepant number of subjects with VOD recognised by investigators and subjects who actually received defibrotide for VOD rescue treatment in study 15-007.*

Summary of the MAH's response
Per Study 15-007 protocol, all participants who were diagnosed with VOD, as per Principal Investigator (PI) assessment, in both defibrotide prophylaxis (DP) and best supportive care (BSC) arms, received defibrotide rescue treatment, except 1 participant who withdrew from study (please see below). As such, no discrepancies are noted.

Overall in study 15-007, a total of 57 participants (57/372, 15.3%) experienced veno-occlusive disease (VOD) by Day +180 post-hematopoietic stem cell transplant (HSCT) as diagnosed by the PI (Module 5.3.5.4/JZP15-007 CSR/Listing 16.2.7.3). Of these, 56 participants received defibrotide as rescue therapy: 25 participants (25/190, 13.2%) in the DP arm and 31 participants (31/182, 17.0%) in the BSC arm (Module 5.3.5.4/JZP15-007 CSR/Table 14.1.2.3 and Figure 2).

One participant 8108-1002, in the BSC arm, was diagnosed with VOD by the PI and subsequently withdrew from the study, based on PI decision, hence rescue defibrotide treatment was not administered.

In summary, there are no discrepancies noted.

Assessment of the MAH's response
The reasoning behind this request was clearly outlined in the AR, pertaining to the presented data on investigators' assessment of VOD vs EPAC assessment which contrasts with the presentation of participant flow.

The MAH asked for a clarification on this topic after the circulation of the LoQ in July 2021; the Rapporteur then replied through a letter to the EMA at 15th July 2021: *it remains unclear why it appears in the participant flow that there were 56 subjects who developed VOD during the prophylaxis phase and received defibrotide as rescue treatment, whereas the decision to start rescue treatment based on the investigator's assessment of VOD was noted in 40 cases of VOD recognised by investigators (Table 11 in AR from CSR Table 14.2.1.11). A further explanation with the responses to the RSI is warranted.*

Despite this, no response to this question has been submitted. However, is assumed that the discrepancy is due to meaning 'prophylaxis phase' as up to Day +180 post-HSCT (or up to Day +100 post-HSCT, see Q4 below) whereas the data on investigator's assessment of VOD pertains to up to Day +30 post-HSCT only (see Q4 below). It is noted that there appears to be remaining inconsistencies with regards to the number of VOD-events as per the investigators' assessment, see Q4 below.

Conclusion

Issue not resolved; *further pursued based on assessment of Q4, see below.*

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

Question 3 *The MAH should discuss the vast difference between investigators and EPAC assessments of VOD and date of VOD diagnosis in more detail, including the diagnostic criteria used and their clinical relevance.*

Summary of the MAH's response

Per protocol, diagnosis of veno-occlusive disease (VOD) was based on Modified Seattle Criteria (MSC) by both blinded EPAC and the PI. The blinded EPAC based their assessment of VOD up to Day +100 post-hematopoietic stem cell transplant (HSCT), per the MSC and on clinical data and information that were provided to them electronically for a retrospective analysis.

A total of 96 participants (DP arm n=53, BSC arm n=43) were assessed to have VOD by the EPAC by Day +100 post-HSCT (

Table **21**). Overall, a total of 56 (DP arm n=25, BSC arm n=31) participants were diagnosed as VOD by PI by Day +100 post-HSCT (Module 5.3.5.4/JZP15-007 CSR/Listing 16.2.7.3).

The EPAC and PI were concordant, in the assessment of VOD, on a total of 190 (53.8%) participants, of which the concordance on the presence of VOD was on 38 (38/353, 10.8%) participants (Table 4). Discordance between PI and EPAC was on 132 (37.4%) participants.

In general, EPAC assessed VOD more often than the PI in both treatment arms.

Table **21** presents additional analysis on the concordance between EPAC and PI diagnosis of VOD by Day +100 post-HSCT, which was based on modified intent-to-treat (mITT) analysis set (n=353). The mITT includes all participants in the ITT Analysis Set (all randomized participants) who underwent HSCT.

Table 21. Concordance between PI and EPAC Assessed VOD by Day +100 Post-HSCT (mITT Analysis Set) (from Table 4 in the Response document)

	DP (N=179)	BSC (N=174)	Total (N=353)[a]
Investigator Assessed VOD/EPAC Assessed VOD			
Yes/Yes	19 (10.6)	19 (10.9)	38 (10.8)
Yes/No	3 (1.7)	0	3 (0.8)
No/Yes	34 (19.0)	24 (13.8)	58 (16.4)
No/No	71 (39.7)	81 (46.6)	152 (43.1)
Yes/Not evaluable	2 (1.1)	0	2 (0.6)
No/Not evaluable	39 (21.8)	30 (17.2)	69 (19.5)
Investigator Assessed VOD/EPAC Assessed VOD = Yes/Yes			
n	19	19	38

	DP (N=179)	BSC (N=174)	Total (N=353)[a]
VOD Diagnosis Dates Match	6 (31.6)	7 (36.8)	13 (34.2)
VOD Diagnosis Dates Do Not Match	13 (68.4)	12 (63.2)	25 (65.8)

Abbreviations: BSC = Best Supportive Care; DP = Defibrotide Prophylaxis; EPAC = Endpoint Adjudication Committee; HSCT = hematopoietic stem cell; VOD = Veno-Occlusive Disease Note: Percentages for Investigator/EPAC agreement were calculated using number of subjects in each arm from the mITT Analysis Set as a denominator. Note: Percentages for matching diagnosis dates were calculated using total number of Yes/Yes agreements in each arm as a denominator.

[a]Of the 353 participants in the mITT Analysis Set, 322 had VOD evaluations included in this concordance analysis. Thirty-one participants were not included in the analysis due to the following reasons, as specified in the Statistical Analysis Plan (SAP; Module 5.3.5.4/JZP15-007 CSR/CSR Section 8.8.6/SAP Section 10.1): 18 participants (DP arm n=9; BSC arm n=9) died and had EPAC assessment as "No VOD"; 3 participants (DP arm n=2; BSC arm n=1) had PI-assessment of VOD as "No VOD" and the EPAC assessment of VOD was prior to the HSCT date; 10 participants (all BSC arm) had VOD diagnosis not confirmed by EPAC. Of the 20 participants in the BSC arm not included in this analysis, 12 participants were diagnosed as having VOD by the PI, but no confirmed or assessed as "No VOD" by EPAC and thus not included in the table.

Source: Table 14.2.2.1.1

Per the Study 15-007 protocol, the diagnosis of VOD was based on the Modified Seattle Criteria or liver biopsy (if performed; this was not mandatory per study protocol). This applied to both investigator diagnosis of VOD and the EPAC assessment for VOD as per the EPAC Charter (Module 5.3.5.4/JZP15-007 CSR/Section 8.9.7). A summary description of the diagnosis of VOD per protocol (Module 5.3.5.4/JZP15-007 CSR/CSR Section 8.1.6/Protocol Section 6.3.1) and the EPAC charter is provided below.

Per study protocol, VOD diagnosis as per the Modified Seattle Criteria required at least 2 of the following criteria:

- Total bilirubin >2 mg/dL or 34 µmol
- Hepatomegaly post-HSCT (with or without right upper quadrant pain) or an increase from baseline in hepatomegaly. Hepatomegaly (both adults and pediatrics) is defined as a >15% increase in

liver size and an absolute increase of at least 1 cm in length in the mid-clavicular line compared with baseline as determined by ultrasonography

· Unexplained weight gain of ≥ 5% above baseline or ascites

The EPAC were blinded to the study treatment. Given the known challenges in VOD diagnosis, the study was set up to provide all relevant clinical information to EPAC to facilitate their assessment of VOD in the absence of being in the clinic with the participants. The MAH made all possible efforts to provide the relevant clinical, laboratory and imaging information, and guidance to standardize the diagnosis of VOD in the study.

Blinded participant characteristics and relevant clinical information in individual participant profile packages were provided to EPAC members, including parameters for Modified Seattle Criteria (bilirubin results, weight, and abdominal ultrasound scans from central imaging reports), transplant data, adverse event (AE) listings, concomitant medications reports, graft-versus-host disease (GvHD) reports, laboratory values, and other clinical information available. The diagnosis of VOD by Modified Seattle Criteria required the participant to have undergone allogeneic (adults or pediatric participants) or autologous (pediatric participants only) HSCT and to have at least 2 of the above-listed Modified Seattle Criteria present OR a liver biopsy (if done) that was positive for VOD.

Each EPAC member was to base their adjudication decision on review of the following as outlined in the EPAC Charter:

· Weight gain ≥5% from baseline (yes/no, date of assessment)

- Total bilirubin >2 mg/dL (yes/no, date of assessment)
- Imaging reports from the central imaging facility providing data regarding liver size and/or ascites
- Physical exam data (assessment of right upper quadrant pain)
- Additional data as clinically indicated
- Biopsy data (any organ)
- For hyperbilirubinemia/liver dysfunction (such as GvHD, intravascular hemolysis, viral infection(s), prior liver disease)
- For ascites and/or weight gain (fluid overload, cardiac failure, capillary leak syndrome)

Challenges in VOD diagnosis are well known and expected, and may be attributed to the following (Carreras 2019):

- Lack of a specific test for the diagnosis of the condition, apart from liver biopsy; while considered as gold standard, it is not frequently performed in clinical practice due to associated risks in such a critically ill population
- Differences in clinical practice and transplant approach between regions and institutions
- Individual physicians' experience and the importance of applying clinical judgement.

It appears that the diagnosis assessment of VOD from by the EPAC was made following strict rules in applying the Modified Seattle Criteria in their decision; this may not have always been optimal based on diagnosis made strictly on data and not being in close monitoring with the patient. It is apparent that more participants were diagnosed with VOD than what actually occurred clinically.

There are other post-transplant conditions that have similar clinical/laboratory features to VOD (Carreras 2019); therefore, clinical judgement and patients' careful monitoring day to day are of paramount importance in the assessment, diagnosis, and management of VOD.

In addition, as evidenced from the literature, Modified Seattle Criteria is more sensitive but less specific for the diagnosis of VOD compared to using Baltimore criteria (14% vs 9%, respectively) (Coppell 2010). The latter is a more stringent criteria that is more likely to diagnose severe VOD.

Furthermore, fluctuations in participants' level of bilirubin and weight post-HSCT were reported, a change that is expected in such a patient population, hence diagnosing VOD strictly on individual parameter levels without a trend can be challenging. It appears that some assessments were made by EPAC on the day the second Modified Seattle Criteria was met regardless of the limited consistency in the changing parameter.

It is worth noting that VOD free survival at Day +30 post HSCT based on PI diagnosis of VOD was numerically higher in the DP arm vs BSC, though not statistically significant as the study was not designed to analyze these data as such (Module 5.3.5.4/JZP15-007 CSR/Table 14.2.1.13).

References:

Carreras E, Dufour C, Mohty M, et al., editors. The EBMT Handbook: Hematopoietic Stem Cell Transplantation and Cellular Therapies [Internet]. 7th edition. Cham (CH): Springer; 2019.

Available from: https://www.ncbi.nlm.nih.gov/books/NBK553942/ doi: 10.1007/978-3-030- 02278-5

Coppell JA, Richardson PG, Soiffer R, et al. Hepatic veno-occlusive disease following stem cell transplantation: incidence, clinical course, and outcome. Biol Blood Marrow Transplant 2010;16(2):157-68.

Assessment of the MAH's response

Per protocol, diagnosis of veno-occlusive disease VOD was based on modified Seattle Criteria by both blinded EPAC and the PI. The blinded EPAC based their assessment of VOD up to Day +100 post-HSCT, per the modified Seattle Criteria and on clinical data and information that were provided to them electronically for a retrospective analysis. The MAH describes the endeavours made to provide the EPAC with all relevant data, including bilirubin results, weight, abdominal ultrasound scans, transplant data, adverse event listings, concomitant medications reports, graft-versus-host disease reports, laboratory values, and other clinical information available. Despite this, the MAH concludes that the EPAC-diagnosed participants with VOD did not have clinically relevant VOD. Since the modified Seattle Criteria relies primarily on objective components, this conclusion is not clearly justified.

The obvious difference between the EPAC and the investigators is that the EPAC was blinded to study treatment whereas investigators were not. Given that the discrepancy between EPAC and investigators was larger in the defibrotide group (with more study subjects diagnosed with VOD by the EPAC) as compared to the best supportive care, these data can also be interpreted that investigators were less able or prone to diagnose VOD, especially in the open-label defibrotide group.

No discussion has been provided regarding any medically relevant differences in characteristics and/or severity of VOD that could potentially explain a discordance of VOD assignment between the EPAC and investigators. The meaning of 'being in close monitoring with the patient' (assumed by the MAH to correlate with a better diagnostic ability) has not been discussed in more detail, such as what data would be collected by such monitoring that were not captured by the laboratory or clinical data that were provided to the EPAC. It is therefore questioned whether such allegedly close monitoring would correlate with a more stringent VOD diagnosis. Furthermore, the data on survival for those diagnosed

with VOD by investigators and those diagnosed with VOD by the EPAC has not been provided, despite being requested; see also Q1d above. It is also noted that the approval of defibrotide for treatment of severe VOD was based on one open-label pivotal trial with a historical control group; thus, for that study, retrospective assessment of VOD was utilised.

As an additional remark, it is noted that in

Table **21** above (from table 4 in the response document) there are 96 events of VOD as assessed by the EPAC and 43 events of VOD as assessed by investigators (38 + 3 + 2) by Day +100 post-HSCT. However, with a reference to listing 16.2.7.3, it is stated that there were 56 participants diagnosed with VOD by investigators by Day +100. The MAH should clarify why these 13 participants are not included in the description of concordance as outlined in Response Table 4 (**LoQ**).

Conclusion

Issue partly resolved; *see overall conclusion and LoQ.*

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

Question 4 *The MAH should present the data on VOD-resolution in subjects diagnosed with VOD (including severity assessment) during study 15-007, divided by those who received defibrotide and those diagnosed vid VOD who did not receive defibrotide, for the entire study population and divided by age groups (paediatric subjects vs adults).*

Summary of the MAH's response

The MAH would like to clarify that the resolution of VOD divided by those participants diagnosed with VOD and received defibrotide and those who were diagnosed with VOD and did not receive defibrotide is not feasible nor a valid analysis from this study.

Resolution of VOD is provided only for those participants who were diagnosed with VOD by the Principal Investigator (PI) and who received rescue treatment. If participants were diagnosed with VOD based on Endpoint Adjudication Committee (EPAC) assessment only but who were not diagnosed also by the PI, then those participants did not receive rescue treatment. These participants had no assessment of VOD resolution performed nor captured in the electronic case report form (eCRF). This is further described below:

Per study protocol, the analysis was based on the retrospective blinded EPAC assessment of VOD; however, administration of rescue defibrotide treatment and resolution of VOD was based on PI assessment of VOD and reporting. Participants designated as having VOD by EPAC but not by PI would not have a resolution recorded, ie would default to not resolved. In addition, per Study 15-007, severity of VOD was not defined; therefore, classification of participants with severe VOD was based on participants diagnosed with VOD who had associated MOD reported by the investigator (Question 1e).

Overall, a total of 56 (pediatric n=30, adult n=26) participants were diagnosed as VOD by PI (Module 5.3.5.4/JZP15-007 CSR/Listing 16.2.7.3) and received defibrotide rescue treatment. Of the 56, a total of 19 participants (pediatric n=9 and adult n=10) were diagnosed with VOD who had a VOD associated MOD reported in eCRF and were also diagnosed with VOD by EPAC (100% concordance). These 19 participants were the total number of participants in the study population (n=372) who had reported VOD associated MOD, and as such can be considered as severe VOD (VOD with MOD). All 19 participants with severe VOD received rescue treatment with defibrotide. The remaining 37 out of the 56 participants had VOD with no reported associated MOD, hence considered non-severe VOD.

Table 22. VOD Resolution for Participants Diagnosed with VOD with MOD by Principal Investigator Who Received Defibrotide Rescue Treatment

SEVERE VOD (VOD with MOD) **Participants with severe VOD (VOD with MOD) and received defibrotide rescue treatment**	
Overall	
Number of participants with severe VOD	19

VOD Resolved	6 (31.6)
VOD Not Resolved	13 (68.4)
Pediatric participants (≤16 years)	
Number of participants	10
VOD Resolved, n (%)	4 (40.0)
VOD Not Resolved, n (%)	6 (60.0)
Adult participants (>16 years)	
Number of participants	9
VOD Resolved, n (%)	2 (22.0)
VOD Not Resolved, n (%)	7 (78.0)
NON-SEVERE VOD **Participants with non-severe VOD and received defibrotide rescue treatment**	
Overall	
Number of participants	37
VOD Resolved	16 (43.0)
VOD Not Resolved	21 (57.0)
Pediatric participants (≤16 years)	
Number of participants	20
VOD Resolved, n (%)	12 (60.0)
VOD Not Resolved, n (%)	8 (40.0)
Adult participants (>16 years)	
Number of participants	17
VOD Resolved, n (%)	4 (24.0)
VOD Not Resolved, n (%)	13 (76.0)

Abbreviations: DF = defibrotide rescue treatment Source: Module 5.3.5.4/JZP15-007 CSR/Listing 16.2.8.3

VOD resolution was provided in the final CSR (Module 5.3.5.4/JZP15-007 CSR/Listing 16.2.8.3).

Of the 19 participants with severe VOD, overall 6 (31.6%) had VOD resolution. In pediatrics, resolution of severe VOD occurred in 4/10 (40%) participants and in adults with severe VOD resolution occurred in 2/9 (22%) participants. In participants with non-severe VOD, resolution occurred in 16/37 (43%). In pediatrics, 12/20 (60%) participants reported VOD resolved, and 4/17 (24%) adult participants reported VOD resolved.

Assessment of the MAH's response

Given the extensive follow-up of participants up to Day +180 post-HSCT according to the protocol, with weekly assessment of VOD and VOD-associated MOD up to day +60 post-HSCT, and at Day +100 post-HSCT and day +180 post-HSCT, there should be data on VOD resolution for all participants diagnosed with VOD during the course of the study.

As discussed above, this SOB pertains to comparative safety data for defibrotide. If there is no difference on resolution of VOD in participants with VOD (regardless if they were diagnosed by

investigators or EPAC), then this is a matter of lack of efficacy, which is not necessarily a safety problem. However, if there was less resolution of VOD among those who received defibrotide for rescue treatment as compared to those who did not receive defibrotide for rescue treatment, then this is a potential safety problem. The Rapporteur fully agrees that no such evaluation was prespecified in the protocol and thus should be interpreted with some caution, however, these data are nevertheless of interest for the currently approved indication. Since there was an assessment of VOD mandated throughout the study as per the protocol at several time points, these data should have been captured and should be presented.

Conclusion

Issue not resolved. *Data to be provided, see LoQ.*

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

Question 5 *One third of the ITT population in study 15-007 had major protocol deviations, primarily related to study "procedures/assessments". The MAH should provide the most frequent reasons for deviation in study procedures/assessments and discuss the integrity of the study given the large number of major protocol deviations*.

Summary of the MAH's response

As described in the Study 15-007 clinical study report (CSR), a total of 123 participants (33.1%) had a major protocol deviation, with a similar proportion of participants in each treatment arm: 64 (33.7%) in the defibrotide prophylaxis (DP) arm and 59 (32.4%) in the best supportive care (BSC) arm (Module 5.3.5.4/JZP15-007 CSR/Section 4.2). Major deviations were primarily categorized as "study procedures/assessments" and were reported for 54 (15.4%) participants overall with a similar incidence in each treatment arm: 26 (13.7%) in the DP arm and 28 (15.4%) in the BSC arm.

None of the major deviations were concluded by the MAH nor the Data Monitoring Committee (DMC) to impact to the data integrity, and no participant was excluded from the analyses due to a major protocol deviation. All deviations were reviewed and assessed per the Protocol Deviation Management Plan (PDMP) (v2.0, 30 June 2020)

Listing 16.2.2.5 presents each major deviation for the category "study procedures/assessments" by participant with the action/resolution of the deviation. Of the 64 major protocol deviations categorized as "study procedures/assessments", the majority (45/64) were due to missed assessments of vital signs — primarily, missed respiratory rate measurements. Other major study procedure/assessment deviations were due to missed assessments of weight (9/64), bilirubin (6/64), and ultrasound (4/64). Study 15-007 required multiple assessment of vital signs (blood pressure, pulse, respiratory rate, and body temperature) as described in the study protocol (Module 5.3.5.4/JZP15-007 CSR/CSR Section 8.1.6/Protocol Section 6.8.3). While this is compatible with the close monitoring performed for transplant patients in clinical practice, per standard of care, only abnormal results are reported. This has led to seemingly numerous missed assessments and hence multiple protocol deviations, which based on the conservative prespecified definition of a vital signs major deviation (please see PDMP below), comprised approximately 15% of major deviations.

Although other major deviations were related to missed bilirubin, weight, and ultrasound, the missed assessments were intermittent, and therefore, had no impact on VOD assessments in those participants. The exception was for 4 participants (2 in each arm) who had major protocol deviations due to multiple missed weight measurements and were marked as 'not evaluable' by (Endpoint Adjudication Committee) EPAC. Both participants in the DP arm had no investigator- assessment of VOD, and were therefore, assessed as 'no VOD' for analysis: Participant 3903- 1004/64 years/Female

discontinued study on Day +19 post-HSCT, and Participant 9707-1005/12 years/Female, discontinued study on Day +5 post HSCT; these early terminations from study might have contributed to the 'not evaluable' assessment by the EPAC. Of the 2 participants in the BSC arm, 1 participant (3906-1001/54 years/Female) was assessed as 'yes VOD' by the PI and discontinued on Day 48 from study and participant 3304-1005/66 years/Female who was assessed as 'no VOD' by the PI and completed the study to end.

Throughout the study, major protocol deviations were reviewed by the sponsor's medical monitor and clinical trial manager and were assessed for impact on participant safety. In addition, DMC members reviewed safety data from all participants enrolled at regular intervals throughout the study as per the DMC charter Section 6.3 Safety Analyses, which states: "The DMC will review safety for the two treatment groups, including AEs, SAEs, clinical laboratory tests, vital signs (including peri-infusional vital signs for patients who receive defibrotide), GvHD, neutrophil and platelet engraftment and graft failure, and Karnofsky/Lansky performance scales." All treatment-emergent adverse events (TEAEs) reported for all participants were made available to Endpoint Adjudication Committee (EPAC) members for their review of VOD assessment for the primary efficacy endpoint.

All deviations reported in the study was reviewed and assessed for minor and major protocol deviations per the Protocol Deviation Management Plan (PDMP) developed in conjunction with the protocol for Study 15-007 (v2.0, 30 June 2020) to outline and define the study-specific requirements for the reporting, review, and assessment of minor and major protocol deviations.

Per this plan, a major protocol deviation was defined as a departure from the approved protocol relating to the conduct of the study which may affect the safety and/or wellbeing of study participants or the study outcomes or data quality. A prospective list of potential major deviation categories with examples of each type was presented in Appendix A of the PDMP. In some cases, continued recurrence of minor deviations were classified as a major deviation. Potential major deviations under the category of "Study Procedures/Assessments and Visit Scheduling" included:

Key missed clinical laboratory tests:

- Bilirubin
  - ≥ 30% during Hospitalization (defined as from HSCT to Day 30)
  - 4 or more consecutive timepoints during Hospitalization

Key missed assessments that contribute to endpoint of safety data, specifically:

- Weight
  - ≥ 30% during Hospitalization (defined as from HSCT to Day 30)
  - 4 or more consecutive timepoints during Hospitalization
- Vital Signs
  - ≥ 30% during Hospitalization (defined as from HSCT to Day 30)
  - 3 or more consecutive timepoints during Hospitalization
  - Note: Missed intensive vital signs (frequent vital signs on the first day of dosing) are considered minor deviations
- Ultrasound
  - ≥ 30% during Hospitalization (defined as from HSCT to Day 30)
  - 2 or more consecutive timepoints during Hospitalization
  - Missed screening/baseline ultrasound
- Efficacy endpoint assessments (acute GvHD, VOD, VOD-associated MOD, survival)
  - ≥ 10% during Hospitalization (defined as from HSCT to Day 30)
  - 3 or more consecutive timepoints during Hospitalization

Key missed visit

- Day +30 post-HSCT visit efficacy assessments

Assessment of the MAH's response

The MAH has clarified the most frequent major protocol deviations; for the category 'study procedures/assessments', this pertains primarily to missed assessments of vital signs, mainly missed respiratory rate measurements. This is not part of the VOD diagnosis criteria used in this study. Other missed assessments were relatively few. It is stated that only abnormal results were reported; this appears not in line with the protocol requirements and would indeed be a very different way of collection of data. It is assumed that this is a typo and that also data within normal limits were actually collected.

Conclusion

Issue resolved.

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

Safety

Question 6. *The MAH should clarify whether subjects treated concomitantly with defibrotide and medications that increase the risk of haemorrhage were adequately captured in study 15-007, and provide outcome data in terms of VOD, bleeding events and TEAEs for these subjects.*

Summary of the MAH's response

In Study 15-007, participants treated concomitantly with defibrotide and medications that increase the risk of haemorrhage were adequately captured. Per the protocol, all medications and therapies taken between baseline and Day +60 post-HSCT were recorded as concomitant medications. Per study protocol, medications that increase the risk of bleeding were prohibited within 24 hours of the first dose of study treatment (defibrotide prophylaxis or as rescue treatment for veno-occlusive disease [VOD]) and throughout the duration of defibrotide administration. Patients were permitted to receive heparin or other anticoagulants for routine central venous line management, and intermittent dialysis or ultrafiltration (Module 5.3.5.4/Study 15-007 CSR/Section 8.1.6/ Section 5.7.6).

As requested by the Agency, analyses have been conducted specifically for participants who received defibrotide concomitantly with any medications that may increase the risk of bleeding (ie, anticoagulants) during both the prophylaxis and rescue phases of the study.

In the Intent-to-Treat (ITT) Analysis Set, 218 patients were identified as having received concomitant anticoagulants as defined by a comprehensive list of medications with antithrombotic or fibrinolytic effects (Table 23): 97 participants in the defibrotide prophylaxis (DP) arm and 121 participants in the best supportive care (BSC) arm. The VOD-free survival rate at Day +30 post-hematopoietic stem cell transplant (HSCT) per the independent Endpoint Adjudication Committee (EPAC), the primary efficacy endpoint of Study 15-007, was slightly higher for participants in the DP arm treated concomitantly with anticoagulants (69.0%) compared to all participants in the DP arm (N=190; 66.8% [Module 5.3.5.4/ Study 15-007 CSR/Table 14.2.1.1]). Therefore, concomitant treatment with anticoagulants did not negatively impact VOD-free survival rates in participants treated with defibrotide. Furthermore, the VOD- free survival rate by Day +30 post-HSCT for participants in the DP arm who were treated concomitantly with defibrotide and anticoagulants (69.0%) was comparable to those in the BSC arm treated with anticoagulants (72.6%), as well as all participants in the BSC arm (N=182; 72.5%). The incidence of VOD/Death by Day +30 post-HSCT was comparable between participants in the DP arm treated concomitantly with anticoagulants (27.8%) and for participants in the BSC arm (24.8%).

Table 23 Primary Efficacy Endpoint: VOD-free Survival by Day +30 post-HSCT for Participants Treated Concomitantly with Medications that Increase the Risk of Hemorrhage (ITT Analysis Set)

Variable, Statistic - patients treated with anti-coagulants	**DP (n=97)**	**BSC (n=121)**
Number of Subjects, n(%)		
Variable, Statistic - patients treated with anti-coagulants	**DP (n=97)**	**BSC (n=121)**
VOD/Death by Day +30 post-HSCT	27 (27.8)	30 (24.8)
Censored	70 (72.2)	91 (75.2)
No VOD/Death by Day +30 post-HSCT	63 (64.9)	75 (62.0)
Other Reason	7 (7.2)	16 (13.2)
KM Estimate of Median Time to VOD/Death in Days (95% CI)	NE	NE
KM Estimate (%) of VOD-free Survival Rate at Day +30 post-HSCT (95% CI)	69.0 (57.5, 78.0)	72.6 (63.1, 80.1)

BSC = best supportive care; CI = confidence interval; DP = defibrotide prophylaxis; HSCT = hematopoietic stem cell transplant; ITT = intent-to-treat; KM = Kaplan-Meier; NE = not estimable; VOD = veno-occlusive disease. n = the number of participants treated concomitantly with medications that increase the risk of hemorrhage within each treatment arm from the ITT Analysis Set. Percentages were calculated with n as a denominator.

Similar results were observed for VOD-free survival rate by Day +100 post-HSCT, where the rate for participants in the DP arm treated concomitantly with anticoagulants (62.6%; Table 24) was comparable to those participants in the BSC arm treated with anticoagulants (60.6%). The incidence of VOD/Death by Day +100 post-HSCT was comparable between participants in the DP arm treated concomitantly with anticoagulants (34% and for participants in the BSC arm (33.1%).

Table 24. VOD-free Survival by Day +100 post-HSCT for Participants Treated Concomitantly with Medications that Increase the Risk of Hemorrhage (ITT Analysis Set)

Variable, Statistic	DP (n=97)	BSC (n=121)
Number of Subjects, n(%)		
VOD/Death by Day +100 post-HSCT	33 (34.0)	40 (33.1)
Censored	64 (66.0)	81 (66.9)
No VOD/Death by Day +100 post-HSCT	41 (42.3)	48 (39.7)
Other Reason	23 (23.7)	33 (27.3)
KM Estimate of Median Time to VOD/Death in Days (95% CI)	NE	NE
KM Estimate (%) of VOD-free Survival Rate at Day +100 post-HSCT (95% CI)	62.6 (51.2, 72.1)	60.6 (49.1, 70.3)

BSC = best supportive care; CI = confidence interval; DP = defibrotide prophylaxis; HSCT = hematopoietic stem cell transplant; ITT = intent-to-treat; KM = Kaplan-Meier; NE = not estimable; VOD = veno-occlusive disease
n = the number of participants treated concomitantly with medications that increase the risk of hemorrhage within each treatment arm from the ITT Analysis Set.
Percentages were calculated with n as a denominator.
Source: Table 14.2.8.2

A total of 95 participants (which represents approximately 50% of the DP arm population) in the Safety Analysis Set (SAS) were identified who received a concomitant anticoagulant in the defibrotide prophylaxis (DP) arm during the prophylaxis phase (Table 14.2.8.3). During the prophylaxis phase, the types of treatment-emergent adverse events (TEAEs) reported and their frequencies were similar between participants treated concomitantly with anticoagulants and the entire DP arm of the SAS. Of the most commonly reported TEAEs, by Preferred Term (PT) in participants treated concomitantly with anticoagulants during the prophylaxis phase (incidence ≥ 15% [

Table **25**]), no individual PT was reported with a ≥ 5% incidence relative to the entire DP arm of the SAS. Since the number of participants who were treated concomitantly with anticoagulants was approximately equal to the number of patients who never received anticoagulants in the DP arm, none of these TEAEs would have occurred with a greater than 10% frequency difference between these 2 sub-groups. Participants treated concomitantly with anticoagulants did not contribute disproportionally to the incidence of the most commonly reported TEAEs. Overall, the safety profile of participants treated concomitantly with anticoagulants was consistent with the known safety profile of defibrotide.

Table 25. Treatment Emergent Adverse Events Reported in ⩾ 15% of Participants Treated Concomitantly with Defibrotide and Anticoagulants During the Prophylaxis Phase (Safety Analysis Set)

Preferred Term (MedDRA)	DP+Anticoagulant N = 95	DP arm N = 181
Diarrhoea	59 (62.1%)	105 (58.0%)
Pyrexia	58 (61.1%)	111 (61.3%)
Nausea	57 (60.0%)	109 (60.2%)
Stomatitis	56 (58.9%)	105 (58.0%)
Vomiting	55 (57.9%)	103 (56.9%)
Hypomagnesaemia	36 (37.9%)	71 (39.2%)
Hypokalaemia	34 (35.8%)	71 (39.2%)
Hypertension	32 (33.7%)	68 (37.6%)
Headache	27 (28.4%)	49 (27.1%)
Abdominal pain	26 (27.4%)	57 (31.5%)
Anaemia	25 (26.3%)	48 (26.5%)
Decreased appetite	24 (25.3%)	50 (27.6%)
Febrile neutropenia	23 (24.2%)	52 (28.7%)
Platelet count decreased	22 (23.2%)	33 (18.2%)
Acute graft versus host disease in skin	20 (21.1%)	30 (16.6%)
Epistaxis	20 (21.1%)	39 (21.5%)
Hypotension	19 (20.0%)	28 (15.5%)
Sinus tachycardia	18 (18.9%)	34 (18.8%)
Blood bilirubin increased	17 (17.9%)	26 (14.4%)
Constipation	17 (17.9%)	34 (18.8%)
Fatigue	16 (16.8%)	24 (13.3%)
Oedema peripheral	16 (16.8%)	26 (14.4%)
Oropharyngeal pain	15 (15.8%)	20 (11.0%)
Rash	15 (15.8%)	29 (16.0%)

Source: Table 14.2.8.3 and Module 5.3.5.4/ Study 15-007 CSR/Table 14.3.1.2

The small sample sizes in the rescue phase of Study 15-007 limits any conclusions on the available safety data. A total of 25 and 31 participants received defibrotide as rescue treatment in the DP and BSC arms, respectively. Of these, 17 of 25 participants (68%) in the DP arm and 25 of 31 participants (80.6%) in the BSC arm were treated concomitantly with anticoagulants (Table 14.2.8.3). Since the majority of participants received treatment with concomitant anticoagulants during the rescue phase, the safety profile of the overall population, in the rescue phase, is largely based on the safety profile of these participants who received concomitant anticoagulant with defibrotide.

In participants treated concomitantly with defibrotide and anticoagulants, the most commonly reported bleeding terms (PTs) during the prophylaxis phase of the study were Epistaxis, Haematuria, Haematochezia, and Mouth haemorrhage (Table 14.2.8.3). The incidences of these PTs were

comparable with those reported in the entire DP arm of the SAS (N=181): Epistaxis (21.1% vs 21.5%, respectively), Haematuria 8.4% vs 9.9%, respectively), Haematochezia (4.2% vs 2.8%, respectively), and Mouth haemorrhage (4.2% vs 2.8%, respectively) (Module 5.3.5.4/ Study 15-007 CSR/Table 14.3.1.2). Since the number of participants who were treated concomitantly with anticoagulants was approximately equal to the number of patients who never received anticoagulants in the DP arm, none of these TEAEs would have occurred with a greater than 3% frequency difference between these 2 sub-groups.

Assessment of the MAH's response

The MAH has clarified that in Study 15-007, participants treated concomitantly with defibrotide and medications that increase the risk of haemorrhage were adequately captured (this is assumed to be despite previous statement that concomitant medications were not captured consistently in the clinical database). Systemic anticoagulation was not allowed in patients treated with defibrotide; per study protocol, medications that increase the risk of bleeding were prohibited within 24 hours of the first dose of study treatment (defibrotide prophylaxis or as rescue treatment for VOD) and throughout the duration of defibrotide administration. Patients were permitted to receive heparin or other anticoagulants for routine central venous line management, and intermittent dialysis or ultrafiltration.

Please note that all medications that may increase the risk of bleeding are not anticoagulants. The large number of subjects that are stated to have been treated with anticoagulants in study 15-007 could thus have been treated with any medication having antithrombotic or fibrinolytic properties. The actual types of such medications have not been discussed, therefore, whether subjects were treated with anticoagulants or not cannot be assessed. Further, it cannot be assessed whether any subjects were treated with systemic anticoagulation or only in relation to CVC management/dialysis/ultrafiltration; the risk of e g bleeding is likely different depending on these different scenarios.

In line with the overall study population, among subjects concomitantly treated with medications that increase the risk of haemorrhage, there was a higher proportion of subjects in the defibrotide group who had VOD/death by Day +30 post-HSCT (27/97 or 27.8%) as compared to the best supportive care (30/121 or 24.8%). The proportion and type of reported TEAEs are comparable between those receiving defibrotide in addition to "anticoagulation" (assumed to be any medication that could increase the risk of bleeding) and the entire defibrotide group.

The current label contraindicates use of thrombolytic therapy concomitantly with defibrotide, whereas use of medicinal products that increase the risk of haemorrhage within 24 hours of Defitelio administration (within 12 hours in the case of unfractionated heparin) is not recommended. For concomitant systemic anticoagulant therapy, careful monitoring is required with consideration to discontinue Defitelio during use of such therapy. Medicinal products that affect platelet aggregation (e.g., NSAIDs) should be administered with care, under close medical supervision, during Defitelio administration. It cannot be assessed whether medications that could increase the risk of bleeding were used in accordance with the label for Defitelio in study 15-007 as no details on the type and administration route of such medications have been provided.

Conclusion

Issue not further pursued.

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

Question 7. *A summary of the TEAEs and the treatment-related TEAEs in study 15-007 should be provided, separated by children and adults using the number of children and adults respectively as the denominator when presenting percentages. Any differences between treatment groups as well as any differences between age groups should be addressed, including any implications for the labelling of adverse reactions.*

Summary of the MAH's response

The summaries of treatment-emergent adverse events (TEAEs) by treatment arm and age subgroup (pediatrics, ≤ 16 years of age; adults, > 16 years of age) have been prepared using the number of participants in each subgroup, respectively, as the denominator to calculate incidences. The results from Study 15-007 demonstrate that the safety of defibrotide is comparable between adults and pediatric subgroups. While some TEAEs were observed as more common in one age subgroup versus the other, there were no trends observed, and results were comparable between the 2 treatment arms of the study. The safety results from Study 15-007 are consistent with the known defibrotide safety profile; accordingly, no changes will be required to the current Summary of Product Characteristics (SmPC) and the Reference safety information (RSI).

A total of 187 pediatric participants (defibrotide prophylaxis (DP) arm, n = 99; best supportive care (BSC) arm n = 88) and 168 adult participants (DP arm, n = 82; BSC arm n = 86) were included in the Safety Analysis Set (SAS). Demographic and baseline characteristics for these subgroups are summarized in Module 5.3.5.4/Study 15-007 CSR/Section 9.1/Table 14.1.4.4 (pediatric) and Table 14.1.4.6 (adults). Treatment-emergent AEs were summarized by system organ class (SOC) and preferred term (PT) and by treatment arm and age subgroup (pediatrics, ≤ 16 years of age; adults, > 16 years of age) in Module 5.3.5.4/Study 15-007 CSR/Section 9.3/Table 14.3.1.4. However, the denominator used for the subgroups in this previously-submitted summary table was the number of participants in the overall population, rather than the number of participants in each subgroup. Table 14.3.1.27 and Table 14.3.1.28, provided at the request of the Agency, summarize the TEAEs and treatment-related TEAEs, respectively, in Study 15-007 by treatment arm and by age subgroups using the number of participants in the respective subgroup as denominator. The most common TEAEs (those occurring in ≥ 20% of participants (by SOC or PT) overall and in any subgroup in either treatment arm) are shown for the prophylaxis and rescue phases in Table 26.

Prophylaxis Phase

Nearly all participants, regardless of age group, had at least 1 TEAE during the prophylaxis phase. The most common TEAE PTs for the pediatric population were similar for the 2 treatment arms during the prophylaxis phase and included Pyrexia, Vomiting, Stomatitis, Nausea, and Diarrhoea. The most common TEAE PTs for the adult population was similar to the pediatric population and similar for the 2 treatment arms during the prophylaxis phase.

In the prophylaxis phase, higher incidences (> 10%) of TEAEs for the pediatric subgroup compared to the adult subgroup were observed for several PTs, eg: Hypomagnesaemia, Platelet Count Decreased, Activated partial thromboplastin time prolonged, Febrile Neutropenia, Pyrexia, Pain, Tachypnoea, and Sinus Tachycardia (Table 14.3.1.27). However, the incidences of these PTs were comparable between the DP and BSC treatment arms within the pediatric subgroup.

In the prophylaxis phase, higher incidences of TEAEs by PT for the adult subgroup compared to the pediatric subgroup were observed including Headache, Back pain, Haemorrhoids, Anxiety, and Insomnia. Similarly, the incidences were comparable between the DP and BSC arms within the adult subgroup.

As expected in this open-label study where the comparator arm consists of supportive care, assessments of treatment relatedness were made only in the DP arm during the prophylaxis phase

(Table 14.3.1.28). During the prophylaxis phase, more adult participants compared to pediatric participants experienced a TEAE assessed as related to defibrotide treatment (pediatric 16 [16.2%]; adult 25 [30.5%]). Treatment-related TEAEs that occurred in ≥ 2% of participants in either age subgroup of the DP arm included Epistaxis (pediatric 4 [4.0%]; adult 4 [4.9%]), Haematochezia (pediatric 3 [3.0%]; adult 1 [1.2%]), Activated partial thromboplastin time prolonged (pediatric 2 [2.0%]; adult 2 [2.4%]), Haematemesis (pediatric 2 [2.0%]; adult 1 [1.2%]), and Gastrointestinal haemorrhage (pediatric 1 [1.0%]; adult 2 [2.4%]).

Rescue Phase

A total of 30 pediatric participants (DP arm, n = 15; BSC arm n = 15) and 26 adult participants (DP arm, n = 10; BSC arm n = 16) were included in the Safety Analysis Set (SAS) of the rescue phase. All participants, regardless of age group, had at least 1 TEAE during the rescue phase (Table 26). The most common TEAE Preferred Terms (PTs) for the pediatric population during the rescue phase included Veno-occlusive disease, Constipation, Vomiting, Hypertension. Worthy of note, for pediatric participants, the incidences of Pyrexia (DP arm [13.3%], BSC arm [53.3%]) and Hypotension (DP arm [0], BSC arm [33.3%]) were greater in the BSC arm vs DP arm. During the rescue phase, both treatment arms received defibrotide; therefore, assessment of relatedness to defibrotide treatment could be made for either arm (Table 14.3.1.28). Only Epistaxis occurred in more than 1 participant within a treatment group (n = 2, BSC arm) — 1 pediatric participant and 1 adult participant. All other PTs were reported for 1 participant each per treatment group and age subgroup.

AESIs (pulmonary hemorrhage, gastrointestinal bleeding, and hypersensitivity reactions) were summarized by age subgroup and presented in M2.7.4 Addendum 1/Section 5.1. During the prophylaxis phase, the incidence of AESI of gastrointestinal bleeding was less than 10% overall. Although, there was a higher incidence of these events in the pediatric subgroup compared with the adult subgroup, the number of events were comparable between the 2 treatment arms in both subgroups (DP arm: n = 10 pediatric [5.5%], n = 6 adult [3.3%]; and BSC arm: n = 10 pediatric [5.7%], n = 4 adult [2.3%]). A similar observation was made during the rescue phase. The higher incidence of bleeding events in the pediatric subgroup is consistent with the current defibrotide SmPC. However, the observation from Study 15-007 with the BSC reference therapy arm indicates that this observation may not be a reflection of defibrotide treatment, but rather, the pediatric subgroup is inherently at a higher risk for some bleeding events.

In conclusion, the above results from study 15-007 demonstrates that the safety of defibrotide is comparable between adults and pediatric subgroups. While some AEs were observed as more common in one age subgroup versus the other, there were no trends observed and results were comparable between the 2 treatment arms of the study.

The safety results from Study 15-007 are consistent with the known defibrotide safety profile; accordingly, no changes will be required to the current SmPC and the RSI.

Table 26. TEAEs by System Organ Class and Preferred Term Occurring in ⩾ 20% of Participants in Either Treatment Arm– Safety Analysis Set, Overall and By Age Group

	DP			BSC		
Study Phase System Organ Class Preferred Term (MedDRA)	**Total n (%)**	**Pediatric (<=16 Years)**	**Adult (>16 Years)**	**Total n(%)**	**Pediatric (<=16 Years)**	**Adult (>16 Years)**
Prophylaxis	**181**	**99**	**82**	**174**	**88**	**86**
Number of Subjects With at Least 1 TEAE	180 (99.4)	99 (100)	81 (98.8)	174 (100)	88 (100)	86 (100)
Gastrointestinal disorders	**176 (97.2)**	**95 (96.0)**	**81 (98.8)**	**166 (95.4)**	**85 (96.6)**	**81 (94.2)**
Nausea	109 (60.2)	57 (57.6)	52 (63.4)	98 (56.3)	54 (61.4)	44 (51.2)
Diarrhoea	105 (58.0)	51 (51.5)	54 (65.9)	106 (60.9)	54 (61.4)	52 (60.5)
Stomatitis	105 (58.0)	62 (62.6)	43 (52.4)	116 (66.7)	62 (70.5)	54 (62.8)
Vomiting	103 (56.9)	64 (64.6)	39 (47.6)	90 (51.7)	59 (67.0)	31 (36.0)
Abdominal pain	57 (31.5)	34 (34.3)	23 (28.0)	45 (25.9)	26 (29.5)	19 (22.1)
Constipation	34 (18.8)	14 (14.1)	20 (24.4)	37 (21.3)	16 (18.2)	21 (24.4)
General disorders and administration site conditions	**143 (79.0)**	**80 (80.8)**	**63 (76.8)**	**146 (83.9)**	**78 (88.6)**	**68 (79.1)**
Pyrexia	111 (61.3)	68 (68.7)	43 (52.4)	111 (63.8)	66 (75.0)	45 (52.3)
Oedema peripheral	26 (14.4)	12 (12.1)	14 (17.1)	26 (14.9)	6 (6.8)	20 (23.3)
Metabolism and nutrition disorders	**134 (74.0)**	**80 (80.8)**	**54 (65.9)**	**129 (74.1)**	**67 (76.1)**	**62 (72.1)**
Hypokalaemia	71 (39.2)	43 (43.4)	28 (34.1)	58 (33.3)	29 (33.0)	29 (33.7)
Hypomagnesaemia	71 (39.2)	47 (47.5)	24 (29.3)	58 (33.3)	34 (38.6)	24 (27.9)
Decreased appetite	50 (27.6)	25 (25.3)	25 (30.5)	48 (27.6)	23 (26.1)	25 (29.1)
Hypocalcaemia	19 (10.5)	12 (12.1)	7 (8.5)	23 (13.2)	19 (21.6)	4 (4.7)
Infections and infestations	**117 (64.6)**	**61 (61.6)**	**56 (68.3)**	**99 (56.9)**	**41 (46.6)**	**58 (67.4)**
Investigations	**116 (64.1)**	**67 (67.7)**	**49 (59.8)**	**109 (62.6)**	**66 (75.0)**	**43 (50.0)**

	DP			BSC		
Study Phase System Organ Class Preferred Term (MedDRA)	**Total n (%)**	**Pediatric (<=16 Years)**	**Adult (>16 Years)**	**Total n(%)**	**Pediatric (<=16 Years)**	**Adult (>16 Years)**
Platelet count decreased	33 (18.2)	23 (23.2)	10 (12.2)	43 (24.7)	30 (34.1)	13 (15.1)
Neutrophil count decreased	17 (9.4)	9 (9.1)	8 (9.8)	26 (14.9)	18 (20.5)	8 (9.3)
Skin and subcutaneous tissue disorders	**116 (64.1)**	**68 (68.7)**	**48 (58.5)**	**104 (59.8)**	**56 (63.6)**	**48 (55.8)**
Respiratory, thoracic and mediastinal disorders	**115 (63.5)**	**66 (66.7)**	**49 (59.8)**	**107 (61.5)**	**55 (62.5)**	**52 (60.5)**
Epistaxis	39 (21.5)	21 (21.2)	18 (22.0)	45 (25.9)	24 (27.3)	21 (24.4)
Blood and lymphatic system disorders	**108 (59.7)**	**60 (60.6)**	**48 (58.5)**	**109 (62.6)**	**56 (63.6)**	**53 (61.6)**
Febrile neutropenia	52 (28.7)	36 (36.4)	16 (19.5)	61 (35.1)	34 (38.6)	27 (31.4)
Anaemia	48 (26.5)	29 (29.3)	19 (23.2)	52 (29.9)	32 (36.4)	20 (23.3)
Thrombocytopenia	31 (17.1)	14 (14.1)	17 (20.7)	27 (15.5)	13 (14.8)	14 (16.3)
Vascular disorders	**95 (52.5)**	**51 (51.5)**	**44 (53.7)**	**77 (44.3)**	**43 (48.9)**	**34 (39.5)**
Hypertension	68 (37.6)	34 (34.3)	34 (41.5)	51 (29.3)	30 (34.1)	21 (24.4)
Nervous system disorders	**62 (34.3)**	**23 (23.2)**	**39 (47.6)**	**57 (32.8)**	**21 (23.9)**	**36 (41.9)**
Headache	49 (27.1)	15 (15.2)	34 (41.5)	35 (20.1)	13 (14.8)	22 (25.6)
Immune system disorders	**61 (33.7)**	**29 (29.3)**	**32 (39.0)**	**64 (36.8)**	**28 (31.8)**	**36 (41.9)**
Acute graft versus host disease in skin	30 (16.6)	10 (10.1)	20 (24.4)	33 (19.0)	10 (11.4)	23 (26.7)
Musculoskeletal and connective tissue disorders	**54 (29.8)**	**25 (25.3)**	**29 (35.4)**	**43 (24.7)**	**13 (14.8)**	**30 (34.9)**
Renal and urinary disorders	**54 (29.8)**	**20 (20.2)**	**34 (41.5)**	**47 (27.0)**	**15 (17.0)**	**32 (37.2)**
Injury, poisoning and procedural complications	**50 (27.6)**	**31 (31.3)**	**19 (23.2)**	**36 (20.7)**	**25 (28.4)**	**11 (12.8)**
Psychiatric disorders	**49 (27.1)**	**18 (18.2)**	**31 (37.8)**	**60 (34.5)**	**19 (21.6)**	**41 (47.7)**
Insomnia	16 (8.8)	4 (4.0)	12 (14.6)	31 (17.8)	9 (10.2)	22 (25.6)

	DP			BSC		
Study Phase System Organ Class Preferred Term (MedDRA)	**Total n (%)**	**Pediatric (<=16 Years)**	**Adult (>16 Years)**	**Total n(%)**	**Pediatric (<=16 Years)**	**Adult (>16 Years)**
Cardiac disorders	**48 (26.5)**	**34 (34.3)**	**14 (17.1)**	**38 (21.8)**	**23 (26.1)**	**15 (17.4)**
Sinus tachycardia	34 (18.8)	28 (28.3)	6 (7.3)	24 (13.8)	18 (20.5)	6 (7.0)
Rescue	**25**	**15**	**10**	**31**	**15**	**16**
Number of Subjects With at Least 1 TEAE	25 (100)	15 (100)	10 (100)	31 (100)	15 (100)	16 (100)
Gastrointestinal disorders	**19 (76.0)**	**13 (86.7)**	**6 (60.0)**	**20 (64.5)**	**10 (66.7)**	**10 (62.5)**
Constipation	7 (28.0)	5 (33.3)	2 (20.0)	2 (6.5)	0	2 (12.5)
Diarrhoea	7 (28.0)	3 (20.0)	4 (40.0)	7 (22.6)	4 (26.7)	3 (18.8)
Abdominal distension	5 (20.0)	3 (20.0)	2 (20.0)	2 (6.5)	1 (6.7)	1 (6.3)
Vomiting	5 (20.0)	4 (26.7)	1 (10.0)	4 (12.9)	2 (13.3)	2 (12.5)
Abdominal pain	4 (16.0)	3 (20.0)	1 (10.0)	4 (12.9)	3 (20.0)	1 (6.3)
Stomatitis	4 (16.0)	1 (6.7)	3 (30.0)	3 (9.7)	2 (13.3)	1 (6.3)
Vascular disorders	**17 (68.0)**	**9 (60.0)**	**8 (80.0)**	**24 (77.4)**	**13 (86.7)**	**11 (68.8)**
Venoocclusive disease	14 (56.0)	7 (46.7)	7 (70.0)	18 (58.1)	9 (60.0)	9 (56.3)
Hypertension	6 (24.0)	4 (26.7)	2 (20.0)	6 (19.4)	1 (6.7)	5 (31.3)
Hypotension	3 (12.0)	0	3 (30.0)	9 (29.0)	5 (33.3)	4 (25.0)
Infections and infestations	**16 (64.0)**	**8 (53.3)**	**8 (80.0)**	**22 (71.0)**	**10 (66.7)**	**12 (75.0)**
Cytomegalovirus infection	3 (12.0)	1 (6.7)	2 (20.0)	4 (12.9)	2 (13.3)	2 (12.5)
Cytomegalovirus viraemia	2 (8.0)	0	2 (20.0)	1 (3.2)	0	1 (6.3)
Sepsis	2 (8.0)	0	2 (20.0)	2 (6.5)	1 (6.7)	1 (6.3)
General disorders and administration site conditions	**13 (52.0)**	**6 (40.0)**	**7 (70.0)**	**20 (64.5)**	**10 (66.7)**	**10 (62.5)**
Pyrexia	6 (24.0)	2 (13.3)	4 (40.0)	11 (35.5)	8 (53.3)	3 (18.8)

	DP			BSC		
Study Phase System Organ Class Preferred Term (MedDRA)	**Total n (%)**	**Pediatric (<=16 Years)**	**Adult (>16 Years)**	**Total n(%)**	**Pediatric (<=16 Years)**	**Adult (>16 Years)**
Chills	3 (12.0)	0	3 (30.0)	0	0	0
Investigations	**13 (52.0)**	**8 (53.3)**	**5 (50.0)**	**16 (51.6)**	**12 (80.0)**	**4 (25.0)**
Blood bilirubin increased	6 (24.0)	3 (20.0)	3 (30.0)	2 (6.5)	1 (6.7)	1 (6.3)
Platelet count decreased	5 (20.0)	4 (26.7)	1 (10.0)	2 (6.5)	1 (6.7)	1 (6.3)
Alanine aminotransferase increased	3 (12.0)	2 (13.3)	1 (10.0)	5 (16.1)	4 (26.7)	1 (6.3)
Aspartate aminotransferase increased	3 (12.0)	2 (13.3)	1 (10.0)	5 (16.1)	4 (26.7)	1 (6.3)
International normalised ratio increased	2 (8.0)	1 (6.7)	1 (10.0)	3 (9.7)	3 (20.0)	0
Cytomegalovirus test positive	1 (4.0)	1 (6.7)	0	3 (9.7)	3 (20.0)	0
Respiratory, thoracic and mediastinal disorders	**13 (52.0)**	**7 (46.7)**	**6 (60.0)**	**18 (58.1)**	**9 (60.0)**	**9 (56.3)**
Pleural effusion	5 (20.0)	2 (13.3)	3 (30.0)	5 (16.1)	2 (13.3)	3 (18.8)
Cough	3 (12.0)	1 (6.7)	2 (20.0)	2 (6.5)	1 (6.7)	1 (6.3)
Epistaxis	3 (12.0)	2 (13.3)	1 (10.0)	6 (19.4)	5 (33.3)	1 (6.3)
Metabolism and nutrition disorders	**12 (48.0)**	**6 (40.0)**	**6 (60.0)**	**12 (38.7)**	**6 (40.0)**	**6 (37.5)**
Hypokalaemia	6 (24.0)	3 (20.0)	3 (30.0)	6 (19.4)	4 (26.7)	2 (12.5)
Hypoalbuminaemia	4 (16.0)	3 (20.0)	1 (10.0)	1 (3.2)	0	1 (6.3)
Decreased appetite	3 (12.0)	1 (6.7)	2 (20.0)	5 (16.1)	3 (20.0)	2 (12.5)
Hypomagnesaemia	3 (12.0)	1 (6.7)	2 (20.0)	3 (9.7)	2 (13.3)	1 (6.3)
Skin and subcutaneous tissue disorders	**12 (48.0)**	**6 (40.0)**	**6 (60.0)**	**12 (38.7)**	**5 (33.3)**	**7 (43.8)**
Rash	3 (12.0)	1 (6.7)	2 (20.0)	0	0	0
Injury, poisoning and procedural complications	**11 (44.0)**	**7 (46.7)**	**4 (40.0)**	**6 (19.4)**	**4 (26.7)**	**2 (12.5)**

	DP			BSC		
Study Phase System Organ Class Preferred Term (MedDRA)	**Total n (%)**	**Pediatric (<=16 Years)**	**Adult (>16 Years)**	**Total n(%)**	**Pediatric (<=16 Years)**	**Adult (>16 Years)**
Transplant failure	4 (16.0)	3 (20.0)	1 (10.0)	0	0	0
Renal and urinary disorders	**10 (40.0)**	**2 (13.3)**	**8 (80.0)**	**16 (51.6)**	**9 (60.0)**	**7 (43.8)**
Acute kidney injury	3 (12.0)	0	3 (30.0)	9 (29.0)	3 (20.0)	6 (37.5)
Haematuria	3 (12.0)	1 (6.7)	2 (20.0)	5 (16.1)	3 (20.0)	2 (12.5)
Blood and lymphatic system disorders	**8 (32.0)**	**3 (20.0)**	**5 (50.0)**	**9 (29.0)**	**6 (40.0)**	**3 (18.8)**
Anaemia	5 (20.0)	2 (13.3)	3 (30.0)	3 (9.7)	1 (6.7)	2 (12.5)
Immune system disorders	**8 (32.0)**	**5 (33.3)**	**3 (30.0)**	**6 (19.4)**	**3 (20.0)**	**3 (18.8)**
Acute graft versus host disease in skin	4 (16.0)	3 (20.0)	1 (10.0)	2 (6.5)	0	2 (12.5)
Nervous system disorders	**8 (32.0)**	**3 (20.0)**	**5 (50.0)**	**9 (29.0)**	**3 (20.0)**	**6 (37.5)**
Tremor	4 (16.0)	2 (13.3)	2 (20.0)	1 (3.2)	0	1 (6.3)
Cardiac disorders	**7 (28.0)**	**3 (20.0)**	**4 (40.0)**	**3 (9.7)**	**3 (20.0)**	**0**
Sinus tachycardia	4 (16.0)	0	4 (40.0)	3 (9.7)	3 (20.0)	0
Psychiatric disorders	**7 (28.0)**	**2 (13.3)**	**5 (50.0)**	**9 (29.0)**	**5 (33.3)**	**4 (25.0)**
Insomnia	2 (8.0)	0	2 (20.0)	0	0	0
Hepatobiliary disorders	**6 (24.0)**	**4 (26.7)**	**2 (20.0)**	**6 (19.4)**	**5 (33.3)**	**1 (6.3)**
Venoocclusive liver disease	5 (20.0)	4 (26.7)	1 (10.0)	3 (9.7)	3 (20.0)	0
Eye disorders	**5 (20.0)**	**4 (26.7)**	**1 (10.0)**	**2 (6.5)**	**0**	**2 (12.5)**
Musculoskeletal and connective tissue disorders	**4 (16.0)**	**1 (6.7)**	**3 (30.0)**	**7 (22.6)**	**3 (20.0)**	**4 (25.0)**
Back pain	2 (8.0)	0	2 (20.0)	1 (3.2)	0	1 (6.3)
Reproductive system and breast disorders	**2 (8.0)**	**1 (6.7)**	**1 (10.0)**	**4 (12.9)**	**0**	**4 (25.0)**

Abbreviations: BSC = best supportive care (arm); DP = defibrotide prophylaxis (arm); MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event. Source: Table 14.3.1.27

Assessment of the MAH's response

The requested data on TEAEs in the paediatric and adult subgroups have been provided. The MAH states that the safety results from Study 15-007 are consistent with the known defibrotide safety profile and that no changes will be required to the current SmPC. In the provided tables 14.3.1.27 and 14.3.1.28, there is no grouping of events describing similar entities which hampers assessment; however, based on the summary of TEAEs occurring in at least 20% of participants during the prophylaxis phase, there are no clear differences between age groups that warrant further investigations.

During the rescue phase however, although it is stated that the proportion of participants who experienced at least one AESI of pulmonary haemorrhage during the rescue phase was similar in the paediatric subgroup and adult subgroup, this is contradicted by the actual data. Again, all subjects received defibrotide for rescue treatment; arm assignment pertains to the randomised arm for the prophylaxis phase only. In the paediatric group, there were 8 events of pulmonary haemorrhage (original DP arm [n = 3; 12.0%], BSC arm [n = 5;16.1%]) whereas in adults, there were 2 events of pulmonary haemorrhage (original DP arm [n = 1; 4.0%], BSC arm [n = 1; 3.2%]). It appears however that 'pulmonary haemorrhage' included epistaxis, which was the actual event behind the majority of events termed 'pulmonary haemorrhage'.

Conclusion

Issue resolved.

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

Question 8. *The MAH is asked to clarify why only 10 of the deaths that occurred in each treatment arm during the "prophylaxis phase" of study 15-007 were included in the presentation of TEAE leading to death up to day +180 post-HSCT; even when adding those who were diagnosed with VOD and died due to adverse events, the figures are not congruent with the overall presentation of death during the study.*

Summary of the MAH's response

For Study 15-007, the seeming discordances in the number of deaths reported as a treatment-emergent adverse event (TEAE) and the total number of deaths in the study are due to the following reasons:

Per Study 15-007 protocol, the collection of TEAEs were defined within a pre-specified period (described below). All deaths and cause of death were captured on the Death electronic case report form (eCRF). Causes of death were not always due to adverse events (AEs). If the fatal event occurred outside the AE reporting period, no fatal AE was captured on the AE eCRF, as it would not be considered as treatment emergent per the protocol. In summary, all deaths were reported; a subset of deaths were also reported as AEs with fatal outcome if the onset date was within the prespecified reporting period.

A total of 65 (defibrotide prophylaxis arm [DP] n=35, best supportive care [BSC] arm n=30) deaths were reported for the entire study population to Day +180 post-HSCT. Of these 65, a total of 46 deaths (DP arm n=23, BSC arm n=23) were due to AEs. Of the 46 deaths with AE as cause of death 40 participants had at least 1 TEAEs with a fatal outcome, and the remaining 6 participants (DP arm n=1, BSC arm n=5) died due to an AE with an onset date outside AE reporting period.

Over the duration of the study, 40 participants had at least 1 TEAE with a fatal outcome:

- Prophylaxis phase: 20 participants (DP n=10 [5.5%]; BSC n=10 [5.7%]).
- Rescue Phase: 20 participants (DP n=12 [12/25; 48.0%]; BSC n=8 [8/31; 25.8%]

In short, deaths associated TEAEs occurred for a similar number of participants between the prophylaxis phase and rescue phase, as well as, between the DP and BSC arms. A detailed summary of the number of adverse events leading to death is described below.

Per the protocol, at a minimum, the investigator recorded all AEs and serious adverse events (SAEs) that occur from the time written informed consent was obtained until screen failure if applicable, or Day +60 post- hematopoietic stem cell transplant (HSCT), regardless of their relationship to study drug or procedure (Module 5.3.5.4/JZP15-007 CSR/Section 8.1.6/Protocol Section 6.8.1.5). Even if the minimum of Day +60 post-HSCT was met, the investigator continued to record all AEs and SAEs that occur within 30 days after the last dose of defibrotide, regardless of their relationship to study drug or procedure. Any SAE assessed as related to defibrotide or study procedures by the investigator was reported regardless of time after study termination.

In Study 15-007, the occurrence of veno-occlusive disease (VOD) and the administration of rescue defibrotide represent a clinical landmark time point for safety. As described in the Statistical Analysis Plan (SAP; Module 5.3.5.4/JZP15-007 CSR/Section 8.8.6), the safety analyses was conducted using 2 study phases, which were defined with respect to the administration of rescue defibrotide, as follows:

<u>Prophylaxis Phase:</u>

If VOD occurred, the prophylaxis phase started on the Baseline date and ends on the day before the start date of rescue defibrotide (ie, rescue treatment start date – 1).

If VOD does not occur, the prophylaxis phase starts on the Baseline date and ends on the date of study completion/early termination.

Rescue Treatment Phase:

For the subset of participants who developed VOD and received rescue defibrotide, the rescue treatment phase began on the start date of rescue defibrotide and ended on the date of study completion/early termination.

Twenty participants in the prophylaxis phase had at least 1 TEAE reported on the AE electronic case report form (eCRF) with a fatal outcome: 10 participants (5.5%) in the defibrotide prophylaxis (DP) arm and 10 participants (5.7%) in the best supportive care (BSC) arm (Module 5.3.5.4/JZP15-007 CSR/Table 14.3.1.14). In addition, 20 participants in the rescue phase had at least 1 TEAEs with a fatal outcome: 12 participants (12/25; 48.0%) in the DP arm and 8 participants (8/31; 25.8%) in the BSC arm. Therefore, overall, 40 participants had at least 1 TEAE that lead to death. The small number of participants in each treatment arm during the rescue phase limits the interpretation of these safety data, as just 1 reported event can dramatically affect the percentage. With the exception of VOD and multiorgan dysfunction (MOD), no specific TEAE PT with a fatal outcome was reported in more than 1 participant during the rescue phase; as such, no trend or association with defibrotide treatment was observed.

All deaths were captured on the Death eCRF, regardless of whether they were captured as a fatal TEAE on the AE eCRF. The cause of death was captured on the Death eCRF; however, if the cause of death was an AE, this was captured as a non-specific event (ie, "adverse event") with no additional field to capture an event term. In addition to the safety analysis of TEAEs leading to death described above, based on the AE eCRF, the MAH prepared an ad hoc summary of all deaths (any cause) by Day +30, Day +100, and Day +180 post-HSCT by treatment arm, which is based upon the Death eCRF (Module 5.3.5.4/JZP15-007 CSR/Table 14.2.5). Through Day +180 post-HSCT, a total of 65 participants died. The proportion of participants who died during the study was similar in the 2 treatment arms (DP arm n=35 [32.1%]; BSC arm, n=30 [29.4%]). Of the 65, a total of 46 participants died due to an AE (unspecified) per the ad hoc analysis (23 participants in each treatment arm).

The seeming discrepancy between the number of participants (n=40 for both treatment arms and both study phases) with a TEAE leading to death, per the safety analysis, and the number of participants with a primary cause of death as AE (n=46), per the ad hoc analysis, is due to the fact that some participants within the study died outside of the protocol-defined AE reporting period as described above, and therefore, the death and cause of death were captured on the Death eCRF, with no fatal AE reported on the AE eCRF.

Despite this discrepancy, individual participant narratives describing all deaths were prepared and provided in Module 5.3.5.4/JZP15-007 CSR/Section 11.

Assessment of the MAH's response

The MAH has clarified that deaths due to AEs were only captured as AEs with fatal outcome if they occurred during the specific AE reporting period, which could thus be different as compared to the overall number of participants with a primary cause of death as AE. The specific AE reporting period was up to Day +60 post-HSCT or up to 30 days after last defibrotide dose; SAEs assessed as related to defibrotide or study procedures by the investigator were however to be reported regardless of time after study termination.

The definition of prophylaxis phase is somewhat different in this response as compared to the definition of the CSR as included in section 8 Safety above, where it was stated that for the overall

safety population, this phase was defined as the period between baseline and start date of rescue defibrotide, if applicable, or the period between baseline and Day +180 post-HSCT if no VOD occurred (assumably based on VOD diagnosed by investigators). During the prophylaxis phase, 10 participants in each treatment arm had a TEAE with a fatal outcome. During the rescue phase, however, there is a clear imbalance between treatment arms. All subjects in the rescue phase received defibrotide, therefore, the impact of the initial randomised groups is less clear, however, it is noted that TEAEs with a fatal outcome occurred in 12 participants (12/25; 48.0%) in the defibrotide arm and 8 participants (8/31; 25.8%) in the best supportive care arm. There is no in-depth discussion on this finding by the MAH, only a statement that the number of participants in each treatment arm is small which limits the interpretation of these data, and that no specific TEAE PT with a fatal outcome was reported in more than 1 participant during the rescue phase with the exception of VOD and MOD (the number of which is however not presented). There could be several possible reasons for this finding; one could be that participants in the best supportive care arm had less severe VOD (since severity, especially whether MOF/MOD is present at diagnosis or not, is known to affect the outcome), however, another reason could be that participants who had already been exposed to defibrotide had a worse prognosis related to the previous defibrotide treatment as such. The MAH should discuss this finding in more detail including any need to include a recommendation to avoid repeated use of defibrotide in the label. Further, as previously requested, the immunogenicity data should be provided. (**LoQ**)

Conclusion

Issue partly resolved; *further discussion on the clear imbalance between the randomised groups regarding TEAEs with a fatal outcome during the rescue phase is warranted.*

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

Question 9 *For all three adverse events of special interest (pulmonary, haemorrhage, gastrointestinal haemorrhage, hypersensitivity) which are also labelled adverse reactions for Defitelio, the reported event rates during rescue treatment appear higher than what would be expected based on the current label. The MAH should discuss these data in relation to the labelled frequencies and propose any label updates if warranted.*

Summary of the MAH's response

The incidence of related treatment emergent adverse events (TEAEs) within the adverse events of special interest (AESI) categories of pulmonary hemorrhage, gastrointestinal hemorrhage, and hypersensitivity occurred at the same or lower frequency categories during both the prophylaxis and rescue phases of Study 15-007 when compared to adverse drug reactions (ADRs) presented in the Summary of Product Characteristics (SmPC). As such, no updates to the ADRs listed in the SmPC or their respective frequencies would be supported by the new data.

When performing a frequency analysis of TEAEs between Study 15-007 and safety data presented in the SmPC, the MAH would like to emphasize the process by which section 4.8 (Undesirable effects) of the SmPC was created. The original tabulated list of adverse reactions in the SmPC included any Preferred Term (PT) assessed as treatment related in at least 2 subjects within a pooled analysis of safety (SAF3 pool, N=419) that included several clinical studies. The frequency categories of each ADR subsequently were determined from the incidence of treatment-related occurrences as well. On a limited basis, which affected approximately a dozen ADRs in the SmPC, synonymous PTs were grouped together and included as single PTs. The frequencies of some ADRs in the SmPC were subsequently updated and increased after comparison with data from the completed T-IND (2006-05) Study.

For the AESI of Pulmonary hemorrhage, the current SmPC only includes Pulmonary haemorrhage as an ADR. In creating the SmPC, the term of Pulmonary alveolar haemorrhage was grouped under Pulmonary haemorrhage, and the frequency was determined as common. The Statistical Analysis Plan for Study 15-007 included a broad range of PTs to use in the analysis for Pulmonary hemorrhage. Bleeding terms of the upper respiratory tract such as Epistaxis were also included in the overall summary table. When excluding Epistaxis, the incidences of bleeding within the lower respiratory tract and the lungs themselves were very low. During the prophylaxis phase of Study 15-007, the incidence of Pulmonary haemorrhage and Pulmonary alveolar haemorrhage TEAEs deemed related to defibrotide treatment were both < 1%, or uncommon, in frequency (Table 27). As expected in this open-label study where the comparator arm consists of supportive care, assessments of treatment relatedness were made only in the DP arm during the prophylaxis phase. The incidence of Pulmonary haemorrhage and Pulmonary alveolar haemorrhage events, regardless of causality, were very low and comparable in the DP and BSC arms. The incidence of these events were also lower in Study 15-007 compared to the SAF3 pool (Table 28). Within the system organ class (SOC) of Respiratory, thoracic and mediastinal disorders, Epistaxis is also listed as a bleeding ADR in the SmPC. This PT occurred with comparable incidence (both common in frequency in Study 15-007 [4.4%] and the SAF3 pool [4%] as a treatment-related TEAE). Epistaxis, regardless of causality, was reported at a higher incidence in Study 15-007 compared to the SAF3 pool (21.5% vs 8%, respectively). However, the incidence of Epistaxis was actually lower in the defibrotide prophylaxis arm (21.5%) than the best supportive care arm (25.9%) within Study 15-007 (Module 5.3.5.4/JZP15- 007 CSR/Table 14.3.1.3), suggesting the incidence is driven by the underlying disease of the study population and the conditioning regimen rather than exposure to defibrotide. During the rescue phase of Study 15-007, the incidences of hemorrhage events within the Respiratory, thoracic and mediastinal disorders SOC were lower than in the prophylaxis phase for both study arms.

Table 27. Incidence of Treatment-Related Pulmonary Haemorrhage TEAEs

System Organ Class Preferred Term (MedDRA)	Study 15-007				SAF3 Pool used for SmPC ADR Determination N=419
	DP arm Prophylaxis Phase N=181	BSC arm Prophylaxis Phase N= 174	DP arm Rescue Phase N=25	BSC arm Rescue Phase N=31	
Respiratory, thoracic and mediastinal disorders					
Epistaxis	8 (4.4%)	-	1 (4.0%)	2 (6.5%)	15 (3.6%)
Haemoptysis	2 (1.1%)	-	0	0	0
Respiratory tract haemorrhage	1 (0.6%)	-	0	0	0
Bronchial haemorrhage	0	-	0	0	0
Pulmonary alveolar haemorrhage	1 (0.6%)	-	0	0	10 (2.4%)
Pulmonary haemorrhage	0	-	0	0	17 (4.1%)

Abbreviations: ADR = adverse drug reaction; BSC = best supportive care; DP = defibrotide prophylaxis; MedDRA = Medical Dictionary for Regulatory Activities; SAF3 = pooled analysis of safety; SmPC = Summary of Product Characteristics; TEAE = treatment-emergent adverse events. Source: Module 5.3.5.4/Study 15-007 CSR/Table 14.3.1.6: Treatment-Related Treatment Emergent Adverse Events Safety Analysis Set; Module 5.3.5.3/Integrated Summary of Safety/ Table 13: All DF-related Adverse Events and Occurrence Rates, SAF3 pool

Table 28. Incidence of Pulmonary Haemorrhage TEAEs Regardless of Causality

System Organ Class Preferred Term (MedDRA)	Study 15-007				SAF3 Pool used for SmPC ADR Determination N=419
	DP arm Prophylaxis Phase N=181	BSC arm Prophylaxis Phase N= 174	DP arm Rescue Phase N=25	BSC arm Rescue Phase N=31	
Respiratory, thoracic and mediastinal disorders					
Epistaxis	39 (21.5%)	45 (25.9%)	3 (12.0%)	6 (19.4%)	34 (8.1%)
Haemoptysis	3 (1.7%)	0	1 (4.0%)	0	1 (0.2%)
Respiratory tract haemorrhage	2 (1.1%)	0	0	0	0
Bronchial haemorrhage	1 (0.6%)	0	0	0	0
Pulmonary alveolar haemorrhage	1 (0.6%)	0	0	0	13 (3.1%)
Pulmonary haemorrhage	1 (0.6%)	1 (0.6%)	0	0	26 (6.2%)

Abbreviations: ADR = adverse drug reaction; BSC = best supportive care; DP = defibrotide prophylaxis; MedDRA = Medical Dictionary for Regulatory Activities; SAF3 = pooled analysis of safety; SmPC = Summary of Product Characteristics; TEAE = treatment-emergent adverse events. Source: Module 5.3.5.4/Study 15-007 CSR/Table 14.3.1.17: Treatment Emergent Adverse Events of Special Interest: Pulmonary Hemorrhage; Module 5.3.5.3/Integrated Summary of Safety/Table 109: All Adverse Events and Occurrence Rates, SAF3 pool

For the AESI of Gastrointestinal hemorrhage, the current SmPC includes several bleeding ADRs under the Gastrointestinal disorders SOC. This includes the PTs of Gastrointestinal haemorrhage, Haematemesis, and Mouth haemorrhage, which are listed as common in frequency, and the PT of Melaena that has a frequency of uncommon. Additionally, in creating the SmPC the terms of Gastric haemorrhage, Haematochezia, and Upper gastrointestinal haemorrhage were grouped together under the PT of Gastrointestinal haemorrhage. The incidences of both treatment-related and all causality bleeding PTs were generally comparable within the SOC of Gastrointestinal disorders between the prophylaxis phase of Study 15-007 and the SAF3 pool (

Table **29** and

Table **30**). All frequency classifications within the SmPC would remain unchanged using the incidence of treatment-related TEAEs in Study 15-007. During the rescue phase of Study 15- 007, the incidence of hemorrhage events within the Gastrointestinal disorders SOC were generally comparable or lower than in the prophylaxis phase for both study arms.

Table 29. Incidence of Treatment-Related Gastrointestinal Haemorrhage TEAEs

System Organ Class Preferred Term (MedDRA)	Study 15-007				SAF3 Pool used for SmPC ADR Determination N=419
	DP arm Prophylaxis Phase N=181	BSC arm Prophylaxis Phase N=174	DP arm Rescue Phase N=25	BSC arm Rescue Phase N=31	
Gastrointestinal disorders					
Haematemesis	3 (1.7%)	-	0	0	3 (0.7%)
Haematochezia	4 (2.2%)	-	0	0	3 (0.7%)
Mouth haemorrhage	1 (0.6%)	-	0	0	2 (0.4%)
Gastrointestinal haemorrhage	3 (1.7%)	-	0	0	17 (4.1%)
Melaena	1 (0.6%)	-	0	0	2 (0.4%)
Lower gastrointestinal haemorrhage	1 (0.6%)	-	0	0	0
Rectal haemorrhage	0	-	1 (4.0%)	0	1 (0.2%)
Upper gastrointestinal haemorrhage	0	-	1 (4.0%)	0	2 (0.4%)
Gastric haemorrhage	0	-	0	0	1 (0.2%)

Abbreviations: ADR = adverse drug reaction; BSC = best supportive care; DP = defibrotide prophylaxis; MedDRA = Medical Dictionary for Regulatory Activities; SAF3 = pooled analysis of safety; SmPC = Summary of Product Characteristics; TEAE = treatment-emergent adverse events. Source: Module 5.3.5.4/Study 15-007 CSR/Table 14.3.1.6: Treatment-Related Treatment Emergent Adverse Events Safety Analysis Set; Module 5.3.5.3/Integrated Summary of Safety/Table 13: All DF-related Adverse Events and Occurrence Rates

Table 30. Incidence of Gastrointestinal Haemorrhage TEAEs Regardless of Causality

System Organ Class Preferred Term (MedDRA)	Study 15-007				SAF3 Pool used for SmPC ADR Determination N=419
	DP arm Prophylaxis Phase N=181	BSC arm Prophylaxis Phase N= 174	DP arm Rescue Phase N=25	BSC arm Rescue Phase N=31	
Gastrointestinal disorders					
Haematemesis	6 (3.3%)	3 (1.7%)	0	0	13 (3.1%)
Haematochezia	5 (2.8%)	2 (1.1%)	1 (4.0%)	1 (3.2%)	4 (0.9%)
Mouth haemorrhage	5 (2.8%)	4 (2.3%)	0	0	5 (1.1%)
Gastrointestinal haemorrhage	4 (2.2%)	1 (0.6%)	0	3 (9.7%)	31 (7.3%)
Melaena	2 (1.1%)	2 (1.1%)	1 (4.0%)	1 (3.2%)	2 (0.4%)
Lower gastrointestinal haemorrhage	1 (0.6%)	0	0	1 (3.2%)	-
Rectal haemorrhage	1 (0.6%)	1 (0.6%)	1 (4.0%)	0	3 (0.7%)
Upper gastrointestinal haemorrhage	0	6 (3.4%)	1 (4.0%)	0	3 (0.7%)
Gastric haemorrhage	0	0	0	0	1 (0.2%)

Abbreviations: ADR = adverse drug reaction; BSC = best supportive care; DP = defibrotide prophylaxis; MedDRA = Medical Dictionary for Regulatory Activities; SAF3 = pooled analysis of safety; SmPC = Summary of Product Characteristics; TEAE = treatment-emergent adverse events. Source: Module 5.3.5.4/Study 15-007 CSR/Table 14.3.1.19: Treatment Emergent Adverse Events of Special Interest: Gastrointestinal Bleeding; Module 5.3.5.3/Integrated Summary of Safety/Table 109: All Adverse Events and Occurrence Rates, SAF3 pool

For the AESI of Hypersensitivity, the current SmPC includes the PTs of Hypersensitivity and Anaphylactic reaction as ADRs, which are assigned uncommon frequency classifications. In the SAF3 pool, no treatment-related events of these PTs were actually reported. These PTs were added to the SmPC due to cases of hypersensitivity, including anaphylaxis being reported from a previously marketed formulation of defibrotide. In addition, the SmPC includes non-specific terms that may represent hypersensitivity reactions, including the PTs of Rash and Pruritis (both classified as common in frequency). In creating the SmPC, the term of Pruritis generalized was grouped under the PT of Pruritis, and the term of Purpura was grouped under the PT of Rash.

The incidence of treatment-related TEAEs were very low (Table 31) during the prophylaxis phase of Study 15-007 and would not change the frequency categorizations of the any of these identified ADRs in the SmPC. The incidences of hypersensitivity reactions and rash, regardless of causality, were higher in Study 15-007 compared to the SAF3 pool (

Table **32**). However, the incidences of these events was again comparable between the defibrotide prophylaxis and best supportive care arms within Study 15-007. During the rescue phase of Study 15-007, the incidences of hypersensitivity and rash/pruritis events were lower than in the prophylaxis phase for both study arms.

Table 31. Incidence of Treatment-Related Hypersensitivity TEAEs

System Organ Class Preferred Term (MedDRA)	Study 15-007				SAF3 Pool used for SmPC ADR Determination N=419
	DP arm Prophylaxis Phase N=181	BSC arm Prophylaxis Phase N= 174	DP arm Rescue Phase N=25	BSC arm Rescue Phase N=31	
Drug hypersensitivity	1 (0.6%)	-	0	0	0
Anaphylactic reaction	1 (0.6%)	-	0	0	0
Hypersensitivity	0	-	0	0	0
Rash	1 (0.6%)	-	0	0	2 (0.4%)
Pruritis	0	-	0	0	2 (0.4%)
Pruritis generalized	0	-	0	0	1 (0.2%)
Purpura	1 (0.6%)	-	0	0	1 (0.2%)

Abbreviations: ADR = adverse drug reaction; BSC = best supportive care; DP = defibrotide prophylaxis; MedDRA = Medical Dictionary for Regulatory Activities; SAF3 = pooled analysis of safety; SmPC = Summary of Product Characteristics; TEAE = treatment-emergent adverse events. Source: Module 5.3.5.4/Study 15-007 CSR/Table 14.3.1.6: Treatment-Related Treatment Emergent Adverse Events Safety Analysis Set; Module 5.3.5.3/Integrated Summary of Safety/Table 13: All DF-related Adverse Events and Occurrence Rates, SAF 3 pool

Table 32. Incidence of Hypersensitivity TEAEs Regardless of Causality

System Organ Class Preferred Term (MedDRA)	Study 15-007				SAF3 Pool used for SmPC ADR Determination N=419
	DP arm| Prophylaxis Phase N=181	BSC arm Prophylaxis Phase N= 174	DP arm Rescue Phase N=25	BSC arm Rescue Phase N=31	
Drug hypersensitivity	7 (3.9%)	6 (3.4%)	0	0	0
Anaphylactic reaction	2 (1.1%)	0	0	0	0
Hypersensitivity	1 (0.6%)	1 (0.6%)	0	0	1 (0.2%)
Rash	29 (16.0%)	20 (11.5%)	3 (12.0%)	0	16 (3.8%)
Pruritis	12 (6.6%)	24 (13.8%)	0	0	8 (1.9%)
Pruritis generalized	12 (6.6%)	10 (5.7%)	0	0	1 (0.2%)
Purpura	2 (1.1%)	2 (1.1%)	0	0	1 (0.2%)

Abbreviations: ADR = adverse drug reaction; BSC = best supportive care; DP = defibrotide prophylaxis; MedDRA = Medical Dictionary for Regulatory Activities; SAF3 = pooled analysis of safety; SmPC = Summary of Product Characteristics; TEAE = treatment-emergent adverse events. Source: Module 5.3.5.4/Study 15-007 CSR/Table 14.3.1.23: Treatment Emergent Adverse Events of Special Interest: Hypersensitivity Reactions; Module 5.3.5.3/Integrated Summary of Safety/Table 109: All Adverse Events and Occurrence Rates, SAF3 pool column

A frequency analysis of treatment-related TEAEs from the AESIs in Study 15-007 compared to the SmPC shows no changes to the frequency categorizations of specific ADRs identified in the label. As such no updates to the list of adverse reactions or their frequencies are required based on the data and results from Study 15-007. When comparing all TEAEs regardless of causality some individual PTs (such as Epistaxis, Drug hypersensitivity, and Rash) did occur with a higher incidence in Study 15-007 than in the SAF3 pool. However, the incidences of these events were comparable between the defibrotide prophylaxis and the best supportive care arms within Study 15-007. The comparable results between the study arms suggests transplant related toxicities, within the proximity of transplant, as the likely contributing factors for the increased incidence in the prophylaxis phase. It is well established that many agents used in conditioning regimens in preparation of the transplant, including myeloablative conditioning, have strong association with hypersensitivity reactions and rash. This differs from prior clinical studies evaluating the treatment of severe VOD where defibrotide is typically initiated at least several weeks after transplant.

Overall, the safety results from Study 15-007 are consistent with the known safety profile of defibrotide.

Assessment of the MAH's response

The MAH has clarified that the incidence of related TEAEs within the AESI categories of pulmonary haemorrhage, gastrointestinal haemorrhage, and hypersensitivity occurred at the same or lower frequency categories during both the prophylaxis and rescue phases of Study 15-007 when compared to ADRs presented in the SmPC, and that no updates to the ADRs listed in the SmPC or their respective frequencies are warranted. Previous prophylaxis studies are included in the SAF3 pool used for SmPC ADR determination; thus, also the prophylaxis data from study 15-007 would be expected to be included. However, the MAH states that all frequency classifications within the SmPC would remain unchanged using the incidence of treatment-related TEAEs in Study 15-007.

Conclusion

Issue resolved.

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

Question 10. *Immunogenicity was an exploratory endpoint for which no data have been provided. However, this is one of the safety concerns addressed by this study. Considering also the difference in hypersensitivity reactions between prophylaxis treatment arms in subjects who developed VOD and were treated with defibrotide, the MAH should provide the immunogenicity data.*

Summary of the MAH's response

The Sponsor is committed to providing the immunogenicity report associated with this study. It is a post-marketing commitment of the US New Drug Application for Defitelio and will be available for submission in Q1 2022.

Assessment of the MAH's response

A commitment to provide these data later is not acceptable. Immunogenicity is one of the safety concerns addressed by this Category 2 study. The requested data should be provided with the Response to the **LoQ**.

Conclusion

Issue not resolved.

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

Question 11. *A summary of all vital sign variables recorded should be presented for the respective treatment group at baseline and at day 30 post-HSCT for the prophylaxis period, and at diagnosis of VOD and at day +30 post-VOD treatment for the rescue treatment period. These data should be provided for the overall study population (safety analysis set) and divided by age groups (paediatric subjects vs adults).*

Summary of the MAH's response

The Safety Analysis Set (SAS) included all participants randomized to the defibrotide prophylaxis (DP) arm who received at least 1 dose of defibrotide (n = 181) and all participants randomized to the best supportive care (BSC) arm who received at least 1 dose of study drug (n = 174) (Module 5.3.5.4/Study 15-007 CSR/Figure 2). Of these, 25 participants in the DP arm and 31 participants in the BSC arm developed VOD, based on investigator assessment, and received defibrotide as rescue treatment.

Table 14.3.3.4.1 provides a summary of vital signs by treatment arm for baseline and Day +30 post-hematopoietic stem cell transplant (HSCT), with changes from baseline to Day +30 post- HSCT. Table 14.3.3.4.2 provides a summary of vital signs by treatment arm at the time of diagnosis of veno-occlusive disease (VOD) and Day +30 post-VOD treatment with changes from VOD diagnosis to Day +30 post-VOD rescue treatment. Both analyses were performed for the overall SAS and by age subgroups (pediatric participants [≤ 16 years old] and adult participants [> 16 years]).

Overall, no clinically meaningful differences in the mean and median weight, temperature, pulse, blood pressure, and respiratory rate were observed between the DP and BSC treatment arms at the timepoints specified. Mean changes in vital signs from baseline to Day +30 post-HSCT were similar between the treatment arms for the overall SAS, as well as both age subgroups. Although some substantial changes in vital signs from VOD diagnosis to Day +30 post-VOD rescue treatment are observed between the 2 treatment arms, the results should be interpreted with caution as the

numbers of participants included the rescue phase were small, and those with vital signs captured at both time points were even smaller.

Assessment of the MAH's response
For vital signs at baseline and at day 30 post-HSCT, changes from baseline were overall small and without clear differences between treatment groups.

However, for the vital signs at VOD diagnosis and 30 days after VOD diagnosis, no assessment can be made due to lack of data. Of the 25 subjects in the randomized defibrotide group who were diagnosed with VOD by investigators, only 6 have blood pressure measurements at the day of VOD diagnosis. For the best supportive care group, 31 subjects were diagnosed with VOD by investigators and 27 have blood pressure measurements at the day of VOD diagnosis. After day +30 post-VOD rescue treatment (n b not post-HSCT), blood pressure measurements were available for 12 subjects in the defibrotide group and 20 subjects in the best supportive care group; there was a mean/median decrease of systolic blood pressure in the defibrotide group of 19/13 mmHg whereas mean/median systolic blood pressure was stable in the best supportive care group; however, there were only 3 subjects for whom blood pressure was available at both day of VOD diagnosis in the defibrotide group (17 in the best supportive care group). For diastolic blood pressure, the overall picture is similar but again, only 3 subjects are available for assessment in the defibrotide group. Also, for pulse rate, respiratory rate, temperature, and weight, there is data for only 6 subjects in the defibrotide group on the day of investigators' VOD diagnosis (as compared to data for 27 subjects in the best supportive care group for pulse rate and temperature, 22 for respiratory rate and 23 for weight) and for only 3 subjects, there are vital sign data both on date of VOD diagnosis and after 30 days in the defibrotide group.

Although it cannot by the protocol be expected to have vital signs data at exactly day +30 after initiation of VOD rescue therapy in all participants, it would be expected to have these data at the day of VOD diagnosis. The paucity of data at the day of VOD diagnosis further entails that a proper assessment of concomitant multiorgan failure/dysfunction cannot be made.

Conclusion

Issue not pursued.

☒No need to update overall conclusion and impact on benefit-risk balance

Question 12. *During the rescue phase, 4 participants (16.0%) in the DP arm and 3 participants (9.7%) in the BSC arm experienced graft failure. The MAH is asked to discuss these findings on graft failure during the rescue phase in more detail, including any possible relation to defibrotide.*

Summary of the MAH's response
At the final analysis of study 15-007, a total of 8 participants in the defibrotide prophylaxis arm (DP; 4 during each of the prophylaxis and rescue phases of the study) and 6 participants in the Best Supportive Care arm (BSC; 3 in each study phase) were reported to have experienced engraftment failure (Module 5.3.5.4/Study 15-007 CSR/Table 14.3.5.3). However, investigating the data on engraftment listing (Listing 16.2.14.2), an additional 3 participants — all in the BSC arm (Participant IDs: 1102-1003, 4904-1001 and 6102-1010) — were reported to have experienced engraftment failure (Prophylaxis phase=1, Rescue phase=2); yet they were not captured in the analysis of graft failure (Table 14.3.5.3).

Per the statistical analysis Plan (SAP) engraftment failure was analyzed based on participants who reported to have both neutrophil and platelet engraftment prior to engraftment failure. As such, although these 3 participants had both neutrophil and platelet engraftment (Module 5.3.5.4/Study 15-007 CSR/Listing 16.2.14.1 and Listing 16.2.14.2), only 1 engraftment occurred prior to the reported date of graft failure hence they were excluded in the final study analysis Table 14.3.5.3. Including the 3 participants described above who were initially excluded from the graft failure analysis based on the SAP definition, a total of 17 participants were had engraftment failure.

Table 33 presents a listing of all participants (n=17) who experienced engraftment failure by treatment arm and study phase (Listing 16.2.14.2). Disease characteristics and relevant clinical information with respect to hematopoietic stem cell transplant (HSCT) engraftment are provided.

From Table 33, in the prophylaxis phase, 4 (2.2%) participants in the DP arm and 5 (2.7%) participants in the BSC arm (including 2 participants in the BSC arm who were excluded from the graft failure in Table 14.3.5.3) arm had engraftment failure.

In the rescue phase, including the 1 additional participant in BSC who experienced graft failure but was not captured in the original analysis, 4 (16.0%) participants in the DP arm and 4 (12.9%) participants in the BSC arm had engraftment failure.

Per the investigator assessment of reported adverse events, no graft failure was related to defibrotide treatment.

In summary, the proportion of participants who experienced graft failure are comparable between the DP arm and the BSC arm in both the prophylactic (4/181 [2.2%] and 5/174 [2.9%], respectively) and rescue phases (4/25 [16%] and 4/31 [12.9%], respectively) of the study. There does not appear to be any relationship between graft failure and defibrotide treatment; rather, the graft failures experienced by participants in Study 15-007 are attributed to the underlying factors that are inherent in the participants and/or related to the type of transplant and known to increase the likelihood of graft failure (eg, allogenic transplant, HLA mismatch).

Table 33. Participants in Study 15-007 with Graft Failure by Study Phase

Participant ID/ Age/Sex	Primary Disease/ VOD Risk Status (risk reason)	Cond Regimen	Type of Graft/ Cell Dose/ Degree of Match	Date of Graft Failure/ Study Day	Relation to Study Drug
Prophylaxis Phase					
Defibrotide Prophylaxis Arm					
8202-1001/ 11 yr/Male	Wilms Tumour/ HR (viral hepatitis)	MAC	Auto PBSC/ 2.48/ NR	2018-01-12/ 28	Unrelated
8204-1001/ 17 yr/Male	HLH HR (high ferritin and transaminase)	MAC	Allo PBSC/ 5.61 8/8	2018-01-10/ 30	Unrelated
9702-1002/ 9 mnth/Male	HLH/ VHR	MAC	Allo PBSC/ 17.2/ 6/10 (had T-cell depletion)	2017-12-19/ 20	Not Reported [a]
9707-1001/ 4 yr/Male	SCID/ VHR	Non-MAC	Allo BM/ 6.72 10/10	2018-03-11/ 81	Not Reported [a]
Best Supportive Care Arm					
3414-1001/ 28 yr/Female	ALL/ VHR	MAC	Allo PBSC/ 5.04/ 10/10 ($CD^{+}34$ selection)	2018-05-23/ 97	Not Applicable [b]
4904-1001/ 49 yr/Male	ALL/ VHR	RIC	Allo PBSC/ 4.56 11/12	2018-07-06/ 29	Not Applicable [b, c]
8204-1005/ 10 yr/Female	Neuroblastoma/ HR	MAC	Auto PBSC/ 12.79/ NR	2018-07-08/ 30	Not Applicable [b]
6102-1010/ 2 yr/Male	X-linked lymphoproliferative disorder/ VHR	MAC	Allo PBSC/ 14.2 5/10 T-cell depletion	2018-07-16/ 25	Not Reported [a, c]
9707-1011/ 13 mnth/Female	Osteopetrosis/ VHR	MAC	Allo BM/ 9.48 10/10	2018-11-11/ 58	Not Applicable [b]

Participant ID/ Age/Sex	Primary Disease/ VOD Risk Status (risk reason)	Cond Regimen	Type of Graft/ Cell Dose/ Degree of Match	Date of Graft Failure/ Study Day	Relation to Study Drug
Rescue Phase					
Defibrotide Prophylaxis Arm					
1304-1008/ 12 mnth/Male	Osteopetrosis/ VHR	MAC	Allo BM/ 15.3/ 5/10	2018-10-12/ 37	Unrelated
6102-1008/ 4 yr/Female	HLH/ VHR	MAC	Allo PBSC/ 8.94/ 5/10 T-cell depletion	2018-04-13/ 22	Unrelated
8202-1012/ 6 yr/M	AML/ HR	MAC	Allo PBSC/ 8.29 5/10	2020-02-07/ 29	Unrelated
8205-1001/ 46 yr/Male	AML/ HR	MAC	Allo PBSC/ 14.96/ 4/8	2018-05-10/ 15	Unrelated
Best Supportive Care Arm					
1102-1003/ 15 yr/Male	ALL/ HR	MAC	Allo BM/ 2/ 10/10 Plasma depleted	2018-07-09/ 101	Not Reported [a, c]
4405-1002/ 4 mnth/Female	Osteopetrosis/ VHR	MAC	Allo BM/ 4.53 5/10	2018-02-05/ 55	Unrelated
8202-1004/ 8 yr/Male	NR/ HR (viral hepatitis)	MAC	Auto PBSC/ 5.45/ NR	2018-04-13/ 30	Not Reported [a]
9003-1001/ 46 yr/Female	ALL/ HR	MAC	Allo PBSC/ 5.85/ 9/10	2018-04-26/"71	Not Reported [a]

Abbreviations: ALL = acute lymphoblasic leukemia; Allo = allogeneic transplant; Auto = autologous transplant; BM = bone marrow; Cond = conditioning; HLH = hemophagocytic lymphohistiocytosis; HR = high risk; ID = identification; MAC = myeloablative conditioning; mnth = months; NR = not reported; PBSC = peripheral blood stem cell transplantation; SCID = severe combined immunodeficiency; VHR = very high risk; VOD = veno-occlusive disease; yr = years.

[a] No adverse event recorded in the Listing 16.2.10.1 All Adverse Events

[b] As expected in this open-label study where the comparator arm consists of supportive care, assessments of treatment relatedness were made only in the Defibrotide Prophylaxis arm during the prophylaxis phase

[c] Experienced graft failure, yet not analyzed as a graft failure due to timing of neutrophil and platelet engraftments.

Source: Listing 16.2.1.3: Stratification at Randomization; Listing 16.2.3.3: Primary Disease History; Listing 16.2.2.2: Defibrotide Prophylaxis Treatment Disposition; Listing 16.2.2.3: Defibrotide Rescue Treatment Disposition; Listing 16.2.14.1: Neutrophil and Platelet Engraftment; Listing 16.2.14.2: Engraftment Status; Listing 16.2.4: Transplant Characteristics; Listing 16.2.5: Medical/Surgical History; Listing 16.2.6.3: Conditioning Regimen for HSCT; Listing 16.2.10.1: All Adverse Events.

Assessment of the MAH's response

It appears that only secondary graft failure was analysed in study 15-007, since per the SAP, engraftment failure was analysed based on participants who reported to have both neutrophil and platelet engraftment prior to engraftment failure.

There was a similar proportion of graft failure in the prophylaxis phase, with 4/181 (2.2%) participants in the defibrotide group and 5/174 (2.7%) participants in the best supportive care group experiencing graft failure. During the rescue phase, however, when all participants received defibrotide, the proportions of graft failures was higher: 8/56 (14%), with more participants in the original defibrotide prophylaxis group as compared to the previous best supportive care group. The conditioning regimen used (majority MAC) could imply a lower risk of graft failure, however, based on the degree of match,

there appears to be more participants with secondary graft failure during the rescue phase who had a lower degree of match which could increase the risk of graft failure and potentially explain the higher proportion of graft failures among these participants.

Conclusion

Issue not further pursued.

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

Question 13 *For abdominal ultrasound results, no summary of data has been provided; the MAH is asked to provide a summary of the findings in each treatment group, for the overall study population (safety analysis set) and divided by age groups (paediatric subjects vs adults).*

Summary of the MAH's response
As per the Study 15-007 protocol (Module 5.3.5.4/Study 15-007 CSR/CSR

Section 8.1.6/Protocol Section 6.3.1.1), VOD diagnosis as per the Modified Seattle Criteria required at least 2 of the following criteria:

- Total bilirubin >2 mg/dL or 34 µmol
- Hepatomegaly post-HSCT (with or without right upper quadrant pain) or an increase from baseline in hepatomegaly. Hepatomegaly (both adults and paediatrics) is defined as a >15% increase in liver size and an absolute increase of at least 1 cm in length in the mid-clavicular line compared with baseline as determined by ultrasonography
- Unexplained weight gain of ≥5% above baseline or ascites (Ascites is defined as the presence of any amount of free fluid greater than trace fluid in the abdomen as determined by ultrasonography in a patient with "ascites absent" at baseline.)

Listing 16.2.22 and Table 14.3.10 provide ultrasound results (liver measurements and ascites) for all participants in the safety analysis set (n=355). Ultrasound measurement were done at defined timepoints per study protocol.

Table 34 presents a summary of the number of participants who had ultrasound abnormalities, per the above protocol definition, from baseline by subgroups of pediatric (≤16 years of age) and adult (>16 years of age) participants, and by treatment arm, as per Agency's request. In addition, abdominal ultrasound results are presented by treatment arm and participant ID for both the pediatric and adult subgroups (Listing 16.2.22). A similar number of participants in each treatment arm had hepatomegaly over the course of the study; and of those, most (~90%) experienced hepatomegaly by Day +30 post-HSCT. Similar results were observed for both the pediatric and adult subgroups. During the study, ascites occurred in fewer participants than hepatomegaly, but similarly, minimal differences were observed between the treatment arms overall or for the age subgroups. The majority of observed ascites occurred by Day +30 post-HSCT. Fewer participants in the DP arm (n=24) reported both ascites and hepatomegaly while on study compared to participants in the BSC arm (n=33). Regardless of treatment arm, most of these observations were by Day +30 post-HSCT. It is worth noting that ascites and hepatomegaly can be experienced by patients post-HSCT and are not specific to VOD.

Table 34. Summary of Participants with Hepatomegaly and Ascites post-HSCT by Treatment Arm and Age Subgroup (Safety Analysis Set)

Variable Time Frame	DP Arm			BSC Arm		
	Total	Pediatric (<=16 Years)	Adult (>16 Years)	Total	Pediatric (<=16 Years)	Adult (>16 Years)
Participants with Hepatomegaly post-HSCT						
Hepatomegaly by Day +30	56	39	17	62	34	28
Hepatomegaly Day +31 - Day +60	19	14	5	23	13	10
Hepatomegaly Day +61 – Day +100	17	13	4	11	8	3
Hepatomegaly Day +101 - Day +180	4	3	1	1	1	0
Overall	63	41	22	68	38	30
Participants with Ascites post-HSCT						
Ascites by Day +30	37	20	17	36	16	20
Ascites Day +31 - Day +60	12	9	3	16	6	10
Ascites Day +61 – Day +100	14	8	6	9	4	5
Ascites Day +101 - Day +180	1	1	0	2	1	1
Overall	48	27	21	46	22	24
Participants with Hepatomegaly and Ascites post-HSCT						
Hepatomegaly and Ascites by Day 30	17	12	5	31	15	16
Hepatomegaly and Ascites Day +31 – Day +60	5	5	0	8	4	4
Hepatomegaly and Ascites Day +61 – Day +100	6	3	3	1	1	0
Hepatomegaly and Ascites Day +101 – Day +180	1	1	0	1	1	0
Overall	24	16	8	33	17	16

Abbreviations: BSC = best supportive care; DP = defibrotide prophylaxis; HSCT = hematopoietic stem cell transplantation
Source: Table 14.3.10

Assessment of the MAH's response

The requested abdominal ultrasound results have been provided; there were no clear differences in findings between treatment groups or age groups (paediatric subjects vs adults).

Conclusion

Issue resolved.

☒No need to update overall conclusion and impact on benefit-risk balance

Question 14. *A summary of the variables recorded for the laboratory findings should be presented for the respective treatment group at baseline and at day 30 post-HSCT for the prophylaxis period, and at diagnosis of VOD and at day +30 post-VOD treatment for the rescue treatment period. These data should be provided for the overall study population (safety analysis set) and divided by age groups (paediatric subjects vs adults).*

Summary of the MAH's response

The Safety Analysis Set (SAS) included all participants randomized to the defibrotide prophylaxis (DP) arm who received at least 1 dose of defibrotide (n = 181) and all participants randomized to the best supportive care (BSC) arm who received at least 1 dose of study drug (n = 174) (Module 5.3.5.4/Study 15-007 CSR/Figure 2). Of these, 25 participants in the DP arm and 31 participants in the BSC arm developed VOD, based on investigator assessment, and received defibrotide as rescue treatment.

Table 14.3.2.5.1, Table 14.3.2.6.1, and Table 14.3.2.7.1 provide summaries of hematology, chemistry, and coagulation laboratory results by treatment arm at baseline and Day +30 post- HSCT, with changes from baseline to Day +30 Post-HSCT. Table 14.3.2.5.2, Table 14.3.2.6.2, and Table 14.3.2.7.2 provide summaries of hematology, chemistry, and coagulation laboratory results, respectively, by treatment arm at the time of diagnosis of VOD and Day +30 post-VOD treatment, with changes from VOD diagnosis to Day +30 Post-VOD rescue treatment. All 6 analyses were performed for the overall SAS and by age subgroups (pediatric participants [≤ 16 years old] and adult participants [> 16 years]).

Overall, no clinically meaningful differences in the mean and median laboratory values were observed between the DP and BSC treatment arms at the timepoints specified. Mean changes in laboratory parameters from baseline to Day +30 post-HSCT were similar between the treatment arms for the overall SAS, as well as both age subgroups. Although some substantial changes in laboratory values from VOD diagnosis to Day +30 post-VOD rescue treatment are observed between the 2 treatment arms, the results should be interpreted with caution as the numbers of participants included the rescue phase were small, and those with laboratory values captured at both time points were even smaller.

Assessment of the MAH's response

For the prophylaxis period and the overall safety analysis set as well as for paediatric subjects vs adults, no clear differences between the treatment groups are noted with regards to haematology, chemistry or coagulation laboratory values.

Laboratory data on the day of VOD diagnosis as well as Day 30 post-VOD rescue treatment initiation is missing for many subjects diagnosed with VOD by investigators; no conclusions can be drawn.

Conclusion

Issue not further pursued.

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

Question 15. *For the additional safety concerns addressed by this study that are not covered by the above RSI, a summary of the main clinical findings should be presented. This pertains to thromboembolic events, patients with pre-existing liver disease, patients with pre-existing renal insufficiency and patients with intrinsic lung disease. Data should be presented for the respective treatment group at baseline and at day 30 post-HSCT for the prophylaxis period, and at diagnosis of VOD and at day +30 post-VOD treatment for the rescue treatment period, and should be provided for the overall study population (safety analysis set) and divided by age groups (paediatric subjects vs adults).*

Summary of the MAH's response

In study 15-007, the safety of defibrotide in patients with pre-existing liver disease, renal insufficiency, or intrinsic lung disease was generally consistent with the known safety profile of defibrotide. The incidence of hemorrhage and thromboembolic events (important identified and potential risks, respectively in the defibrotide Risk Management Plan) were comparable in these subgroups between the DP and BSC arms of the study. In general, the safety profile of defibrotide was comparable between pediatric and adult participants. For events with a difference in incidence between pediatric and adult participants, these differences were consistent between the DP and BSC arms, suggesting age specific explanations rather than an effect of defibrotide. No new safety signals were identified in any of these subgroups overall or for the pediatric and adult age groups.

Participants with pre-existing liver disease

Safety analyses, for the overall population and for pediatric (≤ 16 years old) and adult (> 16 years) subgroups, were performed for participants with pre-existing liver disease. A participant was determined to have pre-existing liver disease if they had any medical condition at baseline within the broad Hepatic disorders standardised MedDRA query (SMQ) or if they had abnormal hepatic function laboratory values at baseline that included asparagine aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin greater than the Upper Limit of Normal (ULN).

During the prophylaxis phase of Study 15-007, a similar number of participants were identified as having pre-existing liver disease in the defibrotide prophylaxis (DP) and best supportive care (BSC) arms (DP n=111; BSC n=110). There were more pediatric than adult participants with pre-existing liver disease in the DP arm (pediatric n=70; adult n=41), and a relatively equal number of pediatric versus adult participants with pre-existing liver disease in the BSC arm (pediatric n=54; adult n=56) during the prophylaxis phase. In the rescue phase of the study, a similar number of participants were identified as having pre-existing liver disease in the DP and BSC arms (DP n=20; BSC n=21). There were also similar numbers of pediatric and adult participants with pre-existing liver disease in both the DP (pediatric n=11; adult n=9) and BSC (pediatric n=10; adult n=11) arms during the rescue phase.

During the prophylaxis phase of study 15-007, the overall safety results in participants with pre-existing liver disease were comparable between the DP and BSC arms. The frequencies of the most common adverse events (defined by occurrence in ≥ 15% of participants in either study arm, see Table 35) were generally comparable between the DP and BSC arms. The most common Preferred Terms (PTs) that were reported with a ≥ 5% higher frequency in the DP arm compared to the BSC arm included Headache, Hypomagnesaemia, Hypotension, Abdominal pain, Hypertension, Hypokalaemia, and Nausea. The most common PTs that were reported by a ≥ 5% higher frequency in the BSC arm compared to the DP arm included Insomnia, Neutrophil count decreased, Platelet count decreased, Acute GvHD in skin, Alanine aminotransferase increased, Diarrhea, Stomatitis, and Constipation. The only PTs reported with a ≥ 10% difference between the DP and BSC arms were Insomnia and Neutrophil count decreased, and these both occurred with higher frequencies in the BSC arm.

Table 35. Treatment Emergent Adverse Events ⩾ 15% in Either the DP or BSC Arm for Subjects with Pre-Existing Liver Disease (Prophylaxis Phase)

	DP			BSC		
Study Phase Preferred Term (MedDRA)	Total n (%)	Pediatric (≤16 yr)	Adult (>16 yr)	Total n (%)	Pediatric (≤16 yr)	Adult (>16 yr)
Prophylaxis	**111**	**70**	**41**	**110**	**54**	**56**
Number of Subjects With at Least 1 TEAE	**111 (100)**	**70 (100)**	**41 (100)**	**110 (100)**	**54 (100)**	**56 (100)**
Stomatitis	70 (63.1)	43 (61.4)	27 (65.9)	76 (69.1)	39 (72.2)	37 (66.1)
Pyrexia	67 (60.4)	46 (65.7)	21 (51.2)	68 (61.8)	41 (75.9)	27 (48.2)
Nausea	65 (58.6)	36 (51.4)	29 (70.7)	59 (53.6)	33 (61.1)	26 (46.4)
Diarrhoea	63 (56.8)	35 (50.0)	28 (68.3)	70 (63.6)	35 (64.8)	35 (62.5)
Vomiting	61 (55.0)	42 (60.0)	19 (46.3)	57 (51.8)	37 (68.5)	20 (35.7)
Hypokalaemia	46 (41.4)	31 (44.3)	15 (36.6)	39 (35.5)	19 (35.2)	20 (35.7)
Hypomagnesaemia	45 (40.5)	33 (47.1)	12 (29.3)	35 (31.8)	20 (37.0)	15 (26.8)
Hypertension	42 (37.8)	27 (38.6)	15 (36.6)	35 (31.8)	21 (38.9)	14 (25.0)
Abdominal pain	38 (34.2)	25 (35.7)	13 (31.7)	31 (28.2)	17 (31.5)	14 (25.0)
Febrile neutropenia	37 (33.3)	28 (40.0)	9 (22.0)	42 (38.2)	22 (40.7)	20 (35.7)
Anaemia	35 (31.5)	24 (34.3)	11 (26.8)	33 (30.0)	19 (35.2)	14 (25.0)
Headache	32 (28.8)	12 (17.1)	20 (48.8)	21 (19.1)	7 (13.0)	14 (25.0)
Decreased appetite	30 (27.0)	16 (22.9)	14 (34.1)	33 (30.0)	16 (29.6)	17 (30.4)
Epistaxis	26 (23.4)	17 (24.3)	9 (22.0)	30 (27.3)	17 (31.5)	13 (23.2)
Platelet count decreased	23 (20.7)	18 (25.7)	5 (12.2)	31 (28.2)	21 (38.9)	10 (17.9)
Sinus tachycardia	22 (19.8)	19 (27.1)	3 (7.3)	18 (16.4)	12 (22.2)	6 (10.7)
Blood bilirubin increased	21 (18.9)	11 (15.7)	10 (24.4)	18 (16.4)	13 (24.1)	5 (8.9)
Hypoalbuminaemia	20 (18.0)	12 (17.1)	8 (19.5)	15 (13.6)	8 (14.8)	7 (12.5)
Neutropenia	20 (18.0)	17 (24.3)	3 (7.3)	18 (16.4)	12 (22.2)	6 (10.7)
Hypotension	19 (17.1)	14 (20.0)	5 (12.2)	12 (10.9)	7 (13.0)	5 (8.9)
Oedema peripheral	18 (16.2)	9 (12.9)	9 (22.0)	19 (17.3)	5 (9.3)	14 (25.0)
Thrombocytopenia	18 (16.2)	12 (17.1)	6 (14.6)	14 (12.7)	7 (13.0)	7 (12.5)
Constipation	17 (15.3)	11 (15.7)	6 (14.6)	23 (20.9)	10 (18.5)	13 (23.2)
Weight increased	17 (15.3)	10 (14.3)	7 (17.1)	12 (10.9)	7 (13.0)	5 (8.9)
Acute graft versus host disease in skin	15 (13.5)	6 (8.6)	9 (22.0)	22 (20.0)	8 (14.8)	14 (25.0)
Alanine aminotransferase increased	11 (9.9)	9 (12.9)	2 (4.9)	17 (15.5)	10 (18.5)	7 (12.5)
Insomnia	9 (8.1)	3 (4.3)	6 (14.6)	23 (20.9)	6 (11.1)	17 (30.4)
Neutrophil count decreased	9 (8.1)	5 (7.1)	4 (9.8)	20 (18.2)	15 (27.8)	5 (8.9)

Abbreviations: BSC = best supportive care; DP = defibrotide prophylaxis; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.
Source: Table 14.3.7.5.1

During the prophylaxis phase, SAEs were reported in a higher percentage of participants with pre-existing liver disease in the DP arm (42.3%) compared to the BSC arm (34.5%) (Table 14.3.7.5.2). There was no specific pattern to the PTs that accounted for this difference. The only SAEs reported in ≥ 3 participants in the DP arm were Pyrexia (5.4%), Respiratory failure (4.5%), and Gastrointestinal haemorrhage (2.7%); and the only SAEs reported in ≥ 3 participants in the BSC arm were Pyrexia (5.5%), Diarrhoea (2.7%), Stomatitis (2.7%), and Acute GvHD in intestine (2.7%).

During the prophylaxis phase, treatment-related AEs were reported in 20.7% of participants with pre-existing liver disease in the DP arm (Table 14.3.7.5.3). The only treatment-related AEs reported in ≥ 3 participants were associated with bleeding and included the PTs of Epistaxis (3.6%), Gastrointestinal hemorrhage (2.7%), and Haematochezia (2.7%). Bleeding events are consistent with the known safety profile of defibrotide. As expected in this open-label study where the comparator arm consists of supportive care, assessments of treatment relatedness were made only in the DP arm during the prophylaxis phase.

During the prophylaxis phase, the overall incidence of bleeding events in participants with pre-existing liver disease was comparable between the DP (44.1%) and BSC (47.3%) arms (Table 14.3.7.5.6). The overall incidence of thromboembolic events in participants with pre-existing liver disease was low and comparable between the DP (3.6%) and BSC (6.4%) arms (Table 14.3.7.5.7).

For participants with pre-existing liver disease during the rescue phase, the most commonly reported PTs in the DP arm were Venoocclusive disease, Diarrhoea, and Pyrexia; and for the BSC arm, Venoocclusive disease, Pyrexia, Acute kidney injury, and Hypotension (Table 36). The most common events in either arm were associated with VOD that developed as a complication of hematopoietic stem cell transplantation (HSCT). While the small populations of participants with pre-existing liver disease in the rescue phase limits the safety analysis, no new safety signals associated with defibrotide were evident.

Table 36. Treatment Emergent Adverse Events ⩾ 20% in Either the DP or BSC Arm for Subjects with Pre-Existing Liver Disease (Rescue Phase)

	DP			BSC		
Study Phase Preferred Term (MedDRA)	Total n (%)	Pediatric (≤16 yr)	Adult (>16 yr)	Total n (%)	Pediatric (≤16 yr)	Adult (>16 yr)
Rescue	20	11	9	21	10	11
Number of Subjects With at Least 1 TEAE	20 (100)	11 (100)	9 (100)	21 (100)	10 (100)	11 (100)
Venoocclusive disease	12 (60.0)	6 (54.5)	6 (66.7)	14 (66.7)	7 (70.0)	7 (63.6)
Diarrhoea	7 (35.0)	3 (27.3)	4 (44.4)	5 (23.8)	2 (20.0)	3 (27.3)
Pyrexia	6 (30.0)	2 (18.2)	4 (44.4)	8 (38.1)	6 (60.0)	2 (18.2)
Blood bilirubin increased	5 (25.0)	3 (27.3)	2 (22.2)	2 (9.5)	1 (10.0)	1 (9.1)
Constipation	5 (25.0)	3 (27.3)	2 (22.2)	1 (4.8)	0	1 (9.1)
Hypertension	5 (25.0)	3 (27.3)	2 (22.2)	4 (19.0)	0	4 (36.4)
Hypokalaemia	5 (25.0)	3 (27.3)	2 (22.2)	4 (19.0)	3 (30.0)	1 (9.1)
Platelet count decreased	5 (25.0)	4 (36.4)	1 (11.1)	2 (9.5)	1 (10.0)	1 (9.1)
Vomiting	5 (25.0)	4 (36.4)	1 (11.1)	3 (14.3)	1 (10.0)	2 (18.2)
Anaemia	4 (20.0)	2 (18.2)	2 (22.2)	3 (14.3)	1 (10.0)	2 (18.2)
Pleural effusion	4 (20.0)	2 (18.2)	2 (22.2)	4 (19.0)	2 (20.0)	2 (18.2)
Acute kidney injury	3 (15.0)	0	3 (33.3)	6 (28.6)	2 (20.0)	4 (36.4)
Hypotension	2 (10.0)	0	2 (22.2)	6 (28.6)	3 (30.0)	3 (27.3)

Abbreviations: BSC = best supportive care; DP = defibrotide prophylaxis; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.
Source: Table 14.3.7.5.1

Within the DP arm, during the prophylaxis phase, some PTs were reported with a ≥ 10% difference between the pediatric and adult subgroups with pre-existing liver disease. Adverse events occurring more frequently for the pediatric subgroup include Sinus tachycardia, Hypomagnesaemia, Febrile neutropenia, Neutropenia, Vomiting, and Platelet count decreased (Table 14.3.7.5.1). Adverse events occurring more frequently for the adult subgroup include Headache, Nausea, Diarrhoea, Acute GvHD in skin, and Decreased appetite. For these events that showed a difference in incidence between pediatric and adult participants, a consistent and comparable difference was also generally seen between the pediatric and adult subgroups within the BSC arm. In the pediatric and adult subgroups of the DP arm, the overall incidence of SAEs (41.4% vs 43.9%, respectively), treatment-related AEs (20.0% vs 22.0%, respectively), and bleeding events (42.9% vs 46.3% respectively) were comparable (Table 14.3.7.5.2, Table 14.3.7.5.3, and Table 14.3.7.5.6, respectively). There were less thromboembolic events in pediatric (1.4%) than adult (7.3%) participants in the DP arm (Table 14.3.7.5.7). The small populations of participants with pre-existing liver disease in the rescue phase limits the safety analysis by age sub-groups during this study phase. Overall, while there were some differences in the safety results between pediatric and adult participants, they were generally consistent and comparable between the DP and BSC arms.

For participants with pre-existing liver disease (overall, adult, and pediatric), Table 14.3.7.1.1 provides a summary of vital signs by treatment arm for baseline and Day +30 post- HSCT, with changes from baseline to Day +30 post-HSCT. Similarly, Table 14.3.7.1.2 provides a summary of vital signs by treatment arm at the time of diagnosis of VOD and Day +30 post-VOD treatment with changes from VOD diagnosis to Day +30 post-VOD rescue treatment. Table 14.3.7.2.1, Table 14.3.7.3.1, and Table 14.3.7.4.1 provide summaries of hematology, chemistry, and coagulation laboratory results, respectively in participants with pre-existing liver disease by treatment arm at baseline and Day +30 post-HSCT, with changes from baseline to Day +30 Post- HSCT. In these same populations, Table 14.3.7.2.2, Table 14.3.7.3.2, and Table 14.3.7.4.2 provide summaries of hematology, chemistry, and

coagulation laboratory results, respectively, by treatment arm at the time of diagnosis of VOD and Day +30 post-VOD treatment, with changes from VOD diagnosis to Day +30 Post-VOD rescue treatment.

Overall, no clinically meaningful differences in the mean and median laboratory values and vital signs were observed between the DP and BSC treatment arms at the timepoints specified. Mean changes in laboratory parameters and vital signs from baseline to Day +30 post-HSCT were similar between the treatment arms for the overall population of participants with pre-existing liver disease, as well as both age subgroups. Although some substantial changes in laboratory values and vital signs from VOD diagnosis to Day +30 post-VOD rescue treatment are observed between the 2 treatment arms, the results should be interpreted with caution as the numbers of participants included the rescue phase were small, and those with laboratory values and vital signs captured at both time points were even smaller.

In this study, the safety of defibrotide in participants with pre-existing liver disease was consistent with the known safety profile of defibrotide and events commonly experienced in the study population. No new safety signals were detected in participants with pre-existing liver disease.

Participants with pre-existing renal insufficiency

Safety analyses, including for the overall population and for pediatric and adult participants, were performed for participants with pre-existing renal insufficiency. A participant was determined to have pre-existing renal insufficiency if they had abnormal renal function labs at baseline, including a serum creatinine elevated above the normal reference range or glomerular filtration rate/creatinine clearance below the normal reference range.

During the prophylaxis phase of Study 15-007, only a small number of participants were identified as having pre-existing renal insufficiency at baseline in either the DP (n=19) or BSC arms (n-25; Table 14.3.8.5.1). There were more adult than pediatric participants with pre-existing renal insufficiency in both the DP (adult n=15; pediatric n=4) and the BSC arms (adult n=21; pediatric n=4) during the prophylaxis phase. In the rescue phase of the study, only 3 participants (all adults) in each treatment arm were identified as having pre-existing renal insufficiency.

The analysis of safety in participants with pre-existing renal insufficiency was limited due to the small populations in Study 15-007. During the prophylaxis phase, the overall safety results in participants with pre-existing renal insufficiency were comparable between the DP and BSC arms (Table 37). The frequencies of the most common adverse events (defined by occurrence in $\geq$ 20% of participants in either study arm) were generally comparable between the DP and BSC arms. The most common PTs that were reported with a $\geq$ 10% higher frequency in the DP arm compared to the BSC arm included Hypertension, Hypoalbuminaemia, Hypomagnesaemia, and Abdominal pain. The most common PTs that were reported by a $\geq$ 10% higher frequency in the BSC arm compared to the DP arm included Stomatitis, Acute GvHD in skin, Fatigue, Acute GvHD in intestine, and Hypotension.

Table 37. Treatment Emergent Adverse Events ⩾ 20% in either the DP or BSC arm for Subjects with Pre-Existing Renal Insufficiency

	DP			BSC		
Study Phase System Organ Class Preferred Term (MedDRA)	Total n (%)	Pediatric (≤16 yr)	Adult (>16 yr)	Total n (%)	Pediatric (≤16 yr)	Adult (>16 yr)
Prophylaxis	19	4	15	25	4	21
Number of Subjects With at Least 1 TEAE	18 (94.7)	4 (100)	14 (93.3)	25 (100)	4 (100)	21 (100)
Diarrhoea	12 (63.2)	2 (50.0)	10 (66.7)	15 (60.0)	2 (50.0)	13 (61.9)
Hypertension	11 (57.9)	3 (75.0)	8 (53.3)	5 (20.0)	0	5 (23.8)
Nausea	10 (52.6)	2 (50.0)	8 (53.3)	13 (52.0)	2 (50.0)	11 (52.4)
Pyrexia	8 (42.1)	2 (50.0)	6 (40.0)	11 (44.0)	2 (50.0)	9 (42.9)
Decreased appetite	7 (36.8)	1 (25.0)	6 (40.0)	9 (36.0)	2 (50.0)	7 (33.3)
Hypomagnesaemia	7 (36.8)	2 (50.0)	5 (33.3)	4 (16.0)	0	4 (19.0)
Stomatitis	7 (36.8)	3 (75.0)	4 (26.7)	17 (68.0)	4 (100)	13 (61.9)
Vomiting	7 (36.8)	2 (50.0)	5 (33.3)	11 (44.0)	3 (75.0)	8 (38.1)
Abdominal pain	6 (31.6)	2 (50.0)	4 (26.7)	4 (16.0)	0	4 (19.0)
Febrile neutropenia	6 (31.6)	3 (75.0)	3 (20.0)	8 (32.0)	2 (50.0)	6 (28.6)
Hypokalaemia	6 (31.6)	3 (75.0)	3 (20.0)	7 (28.0)	0	7 (33.3)
Constipation	5 (26.3)	2 (50.0)	3 (20.0)	8 (32.0)	1 (25.0)	7 (33.3)
Epistaxis	5 (26.3)	1 (25.0)	4 (26.7)	9 (36.0)	2 (50.0)	7 (33.3)
Headache	5 (26.3)	0	5 (33.3)	7 (28.0)	0	7 (33.3)
Hypoalbuminaemia	5 (26.3)	2 (50.0)	3 (20.0)	1 (4.0)	0	1 (4.8)
Anaemia	4 (21.1)	1 (25.0)	3 (20.0)	4 (16.0)	1 (25.0)	3 (14.3)
Cytomegalovirus infection	4 (21.1)	1 (25.0)	3 (20.0)	6 (24.0)	0	6 (28.6)
Oedema peripheral	4 (21.1)	2 (50.0)	2 (13.3)	5 (20.0)	0	5 (23.8)
Acute graft versus host disease in intestine	1 (5.3)	0	1 (6.7)	5 (20.0)	0	5 (23.8)
Fatigue	1 (5.3)	0	1 (6.7)	6 (24.0)	0	6 (28.6)
Hypotension	1 (5.3)	0	1 (6.7)	5 (20.0)	1 (25.0)	4 (19.0)
Acute graft versus host disease in skin	0	0	0	7 (28.0)	1 (25.0)	6 (28.6)

Abbreviations: BSC = best supportive care; DP = defibrotide prophylaxis; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.
Source: Table 14.3.8.5.1

Serious adverse events were reported in similar percentages of participants with pre-existing renal insufficiency in the DP arm (31.6%) compared to the BSC arm (32%) during the prophylaxis phase (Table 14.3.8.5.2). No specific PT was reported as an SAE in more than 2 participants. A total of 6 participants (31.6%) reported a treatment related AE in the DP arm during the prophylaxis phase (Table 14.3.8.5.3). Consistent with the known safety profile of defibrotide, the majority of treatment related AEs represented bleeding events: Epistaxis (n=2) and Haemorrhage subcutaneous, Angina bullosa haemorrhagic, Gingival bleeding, and Catheter site haemorrhage [n=1 each]). As expected in

this open-label study where the comparator arm consists of supportive care, assessments of treatment relatedness were made only in the DP arm during the prophylaxis phase.

During the prophylaxis phase, the overall incidence of bleeding events in participants with pre-existing renal insufficiency was comparable between the DP (57.9%) and BSC (52.0%) arms (Table 14.3.8.5.6). The overall incidence of thromboembolic events in participants with pre-existing liver disease was comparable between the DP (10.5%) and BSC (12.0%) arms (Table 14.3.8.5.7). The small numbers of participants with pre-existing renal insufficiency during the rescue phase limits the analysis of safety during this phase of the study.

An analysis of the safety of defibrotide in pediatric participants with pre-existing renal insufficiency at baseline is limited by the fact that overall only 4 such participants were identified in either arm of Study 15-007, with no pediatric participants receiving rescue treatment.

For participants with pre-existing renal insufficiency (overall, adult, and pediatric), Table 14.3.8.1.1 provides a summary of vital signs by treatment arm for baseline and Day +30 post-HSCT, with changes from baseline to Day +30 post-HSCT. Similarly, Table 14.3.8.1.2 provides a summary of vital signs by treatment arm at the time of diagnosis of veno-occlusive disease (VOD) and Day +30 post-VOD treatment with changes from VOD diagnosis to Day +30 post-VOD rescue treatment. Table 14.3.8.2.1, Table 14.3.8.3.1, and Table 14.3.8.4.1 provide summaries of hematology, chemistry, and coagulation laboratory results, respectively, in participants with pre-existing renal insufficiency by treatment arm at baseline and Day +30 post- HSCT, with changes from baseline to Day +30 Post-HSCT. In these same populations, Table 14.3.8.2.2, Table 14.3.8.3.2, and Table 14.3.8.4.2 provide summaries of hematology, chemistry, and coagulation laboratory results, respectively, by treatment arm at the time of diagnosis of VOD and Day +30 post-VOD treatment, with changes from VOD diagnosis to Day +30 Post- VOD rescue treatment.

Although some substantial changes in laboratory values and vital signs from baseline to Day +30 post-HSCT and from VOD diagnosis to Day +30 post-VOD rescue treatment are observed between the 2 treatment arms, the results should be interpreted with caution as the numbers of participants with pre-existing renal insufficiency is very small, and those with laboratory values and vital signs captured at both time points were even smaller.

In this study, the safety of defibrotide in participants with pre-existing renal insufficiency was consistent with the known safety profile of defibrotide and events commonly experienced in the study population. While the safety analysis was limited by the small number of participants with pre-existing renal insufficiency, no new safety signals were detected in these participants.

Participants with pre-existing intrinsic lung disease

Safety analyses were performed for participants (overall, pediatric, and adult populations) with pre-existing intrinsic lung disease. A patient was determined to have pre-existing intrinsic lung disease if they had any medical condition at baseline within the High Level Group Terms (HLGTs) of Bronchial disorders (excl neoplasms), Congenital respiratory tract disorders, Lower respiratory tract disorders (excl obstruction and infection), Neonatal respiratory disorders, Respiratory disorders NEC, and Respiratory tract neoplasms.

During the prophylaxis phase of Study 15-007, only a small number of participants were identified as having pre-existing intrinsic lung disease at baseline in either the DP (n=8) or BSC arms (n=9; Table 14.3.9.5.1). In the prophylaxis phase, there were more pediatric than adult participants with pre-existing intrinsic lung disease in the DP arm (pediatric n=7; adult n=1) and less pediatric than adult participants in the BSC arm (pediatric n=3; adult n=6). Few participants with pre-existing intrinsic lung were included in the rescue phase (DP n=1; BSC n=2).

The analysis of safety in participants with pre-existing intrinsic lung disease was limited due to the very small populations in Study 15-007. During the prophylaxis phase, for patients with pre-existing intrinsic lung disease in the DP arm, the most commonly PTs reported included Hypokalaemia (n=6), Pyrexia (n=5) and Anaemia, Neutropenia, and Hypomagnesaemia (n=4 each) (Table 14.3.9.5.1). For the BSC arm, the most common reported PTs included Stomatitis (n=6) and Diarrhoea, Epistaxis, Hypomagnesaemia, and Platelet count decreased (n=4 each).

During the prophylaxis phase, SAEs were reported in 4 participants (50%) with pre-existing intrinsic lung disease in the DP arm and 2 participants (22.2%) in the BSC arm (Table 14.3.9.5.2). No PT was reported as serious in more than 1 participant in the DP arm. Treatment-related AEs were reported in 2 participants with intrinsic lung disease in the DP arm of the prophylaxis phase; events included Cerebral haemorrhage and Haemoptysis (Table 14.3.9.5.3), consistent with the known safety profile of defibrotide. As expected in this open-label study where the comparator arm consists of supportive care, assessments of treatment relatedness were made only in the DP arm during the prophylaxis phase.

An analysis of the safety of defibrotide during the rescue phase and in pediatric versus adult participants with pre-existing intrinsic lung disease is limited by the small populations.

For participants with pre-existing lung disease, Table 14.3.9.1.1 provides a summary of vital signs by treatment arm for baseline and Day +30 post-HSCT, with changes from baseline to Day +30 post-HSCT. Similarly, Table 14.3.9.1.2 provides a summary of vital signs by treatment arm at the time of diagnosis of VOD and Day +30 post-VOD treatment with changes from VOD diagnosis to Day +30 post-VOD rescue treatment. Table 14.3.9.2.1, Table 14.3.9.3.1, and Table 14.3.9.4.1 provide summaries of hematology, chemistry, and coagulation laboratory results, respectively, in participants with pre-existing lung disease by treatment arm at baseline and Day +30 post-HSCT, with changes from baseline to Day +30 Post-HSCT. In these same populations, Table 14.3.9.2.2, Table 14.3.9.3.2, and Table 14.3.9.4.2 provide summaries of hematology, chemistry, and coagulation laboratory results, respectively, by treatment arm at the time of diagnosis of VOD and Day +30 post-VOD treatment, with changes from VOD diagnosis to Day +30 Post-VOD rescue treatment.

Although some substantial changes in laboratory values and vital signs from baseline to Day +30 post-HSCT and from VOD diagnosis to Day +30 post-VOD rescue treatment are observed between the 2 treatment arms, the results should be interpreted with caution as the numbers of participants with pre-existing intrinsic lung disease are very small, and those with laboratory values and vital signs captured at both time points were even smaller.

While very few participants with pre-existing intrinsic lung disease received defibrotide in this study, limiting the analysis of safety, no new safety signals were detected in these participants.

Assessment of the MAH's response

The MAH states that in study 15-007, the safety of defibrotide in patients with pre-existing liver disease, renal insufficiency, or intrinsic lung disease was generally consistent with the known safety profile of defibrotide, and that the incidence of haemorrhage and thromboembolic events (important identified and potential risks, respectively in the defibrotide RMP) were comparable in these subgroups between the DP and BSC arms of the study as well as between paediatric and adult participants; differences in incidence between paediatric and adult participants were consistent between the DP and BSC arms, suggesting age specific explanations rather than an effect of defibrotide. No comparison between the population who had the respective disease at baseline and the entire safety population in study 15-007 has been provided.

For liver disease, this was defined as any medical condition at baseline within Hepatic disorders or if they had abnormal hepatic function laboratory values at baseline including AST, ALT, or total bilirubin greater than ULN. This definition is considered very broad as especially laboratory fluctuations in liver function tests are common also necessarily relate to underlying liver disease. Based on this definition, the majority of subjects in Study 15-007 had pre-existing liver disease; 111 subjects in the defibrotide group (out of 190 randomised subjects) and 110 subjects in the best supportive care group (out of 182 randomised subjects). To aid in assessment of this issue, an analysis of subjects in study 15-007 who had pre-existing liver disease based on a defined medical condition of hepatic disorder should be provided. The safety profile should be discussed not only in relation to best supportive care but also in relation to the overall safety population (including a division by paediatric and adult subjects). (**LoQ**)

For pre-existing renal insufficiency, it is found reasonable to consider participants with abnormal renal function tests at baseline, although this is also considered a somewhat broad definition that will capture also those with a transient decrease in glomerular filtration. Nevertheless, rather few subjects were identified as having pre-existing renal insufficiency; 19 subjects in the defibrotide group and 25 subjects in the best supportive care group. Some findings are of interest, including the discrepancy in hypertension and hypomagnesaemia that were more frequently reported in both paediatric and adult subjects who received defibrotide as compared to best supportive care among subjects with pre-existing renal insufficiency, as well as hypokalaemia that was observed in 3 out of 4 paediatric subjects in the defibrotide group and 0 of the 4 paediatric subjects in the best supportive care group. These findings should be discussed in more detail, including a discussion in relation to the overall safety population (including a division by paediatric and adult subjects). (**LoQ**)

There were few participants with pre-existing intrinsic lung disease at baseline: 8 subjects in the defibrotide group and 9 subjects in the best supportive care group. Despite that the numbers are few, also for this safety concern, the MAH is asked to discuss the safety findings in relation to the overall safety population. (**LoQ**)

Conclusion

Issue partly resolved.

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

SmPC

Question 16. *Since previous prophylactic studies have been included in the SmPC and since study 15-007 also includes study data on treatment with defibrotide for VOD as well as paediatric data, the SmPC sections 4.8 and 5.1 should be updated to include data from study 15-007.*

Summary of the MAH's response

The MAH acknowledges the request to update the mentioned sections of the SmPC with the data from study 15-007 and provides the following response per section:

4.8

- No changes to the ADR table will be proposed. Even though the patient population in Study 2004-000592-33 is similar to that of the PVOD study, the decision to further pool the table would not be in alignment with the indicated population of the label. At the time of the original MAA, there was

limited safety data available under the indication of treatment of severe VOD. Inclusion of data in other indications, such as PVOD, provided a more robust safety analyses for the SmPC. However, extensive safety data is now available from multiple sources, such as the completed phase III treatment-IND Study (Study 2006-05) and years of safety reports from post-marketing use, which have both confirmed the known safety profile of defibrotide. As such, the inclusion of data in unapproved indications is no longer warranted, in particular since no new safety signals have been identified in Study 15-007. Furthermore, the MAH would not consider it appropriate to pool the data from the VOD treatment and the VOD prevention studies, given the differences in study designs. Specifically, the administration of Defitelio for treatment typically occurs several weeks after transplant, unlike the current study.

- In regards to the pediatric sub-section, again no updates will be proposed. The current SmPC describes an increased incidence of any bleeding events in the defibrotide group compared with the treatment group in the paediatric prevention study at 25 mg/kg/day (Study 2004-000592-33). In Study 15-007, the incidence of pulmonary hemorrhage events were generally comparable between pediatric and adult participants (12.7% vs 11.6%, respectively [Module 5.3.5.4/JZP15-007 CSR/Table 14.3.1.18]) during the prophylaxis phase. The incidence of gastrointestinal bleeding events were low overall, but moderately higher in pediatric versus adult participants (5.5% vs 3.3%, respectively [Module 5.3.5.4/JZP15-007 CSR/Table 14.3.1.20]). However, differences in the incidence of bleeding events between pediatric and adult participants were consistent between the DP and BSC arms of the study, suggesting defibrotide was not a contributing factor. Overall, no new safety signals were detected in the pediatric population of Study 15-007.

5.1

- A summary of the efficacy results from the primary endpoint is now provided.

- In the pediatric sub-section although not directly associated with Study 15-007 the MAH has updated this section to clarify that the efficacy and safety of Defitelio use has been identified in several studies other than the prevention study. Studies being: 2005-01 Pivotal study, 2006-05 T-IND (Full CSR) and 99-118: Dose finding

Assessment of the MAH's response

The argumentation that safety data from study 15-007 should not be included for the pooled safety data in section 4.8 is somewhat difficult to follow, given that at least one previous prevention-study has been included in that pool. However, the MAH has previously stated that the safety data from study 15-007 are in line with the label for section 4.8. Thus, no amendments are warranted.

For section 5.1, the proposed summary is not sufficient. The findings form study 5.1 should be provided in an unbiased manner including actual numbers for the relevant data. This pertains primarily to the results from the primary efficacy endpoint, but also other relevant data, especially safety data, could be of clear interest for prescribers; the actual data to include will be further assessed within the next round depending on the data presented with responses to the 2nd LoQ.

For the paediatric sub-section, the proposed amendments are not fully accepted; see attached SmPC with comments.

Conclusion

Issue partly resolved; *see attached SmPC with comments.*

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

13. 2nd Request for supplementary information

13.1. Major objections

Clinical aspects

Safety

1. The numerical imbalance in study 15-007 on mortality both during the prophylaxis phase, with a higher mortality in the defibrotide group as compared to best supportive care, as well as during the rescue phase, especially among those initially randomised to defibrotide, should be further addressed. These data are in line with previous prophylaxis data indicating increased mortality with defibrotide, particularly in the paediatric population. The response should include the following:

a. The survival data separated by subjects diagnosed with VOD during study 15-007 who received defibrotide and those diagnosed with VOD who did not receive defibrotide. Any difference should be discussed, including any differences in clinical findings between these groups that could be of relevance.

b. A discussion on the findings of higher mortality in the rescue phase among those initially randomised to defibrotide as compared to those initially randomised to best supportive care, including any differences in clinical findings between these groups that could be of relevance.

c. A discussion of the mortality findings during both prophylaxis and treatment of VOD in study 15-007 in relation to the totality of data on mortality based on relevant previous prophylaxis studies and VOD-treatment studies. This should include whether there are any clinical characteristics that could be relevance in relation to mortality risk as well as a separate discussion on paediatric patients.

13.2. Other concerns

Clinical aspects

Efficacy

2. In table 4 in the response document, there are 96 events of VOD as assessed by the EPAC and 43 events of VOD as assessed by investigators (38 + 3 + 2) by Day +100 post-HSCT. However, with a reference to listing 16.2.7.3, it is stated that there were 56 participants diagnosed with VOD by investigators by Day +100. The MAH should clarify why these 13 participants are not included in the description of concordance between EPAC and investigators as outlined in Response Table 4.

Safety

3. Data on VOD-resolution in subjects diagnosed with VOD during study 15-007 should be provided, divided by those who received defibrotide and those diagnosed with VOD who did not receive defibrotide, for the entire study population and divided by age groups (paediatric subjects vs adults).

4. The immunogenicity data should be provided within this procedure.
5. An analysis of subjects in study 15-007 who had pre-existing liver disease based on a defined medical condition of hepatic disorder at baseline should be provided. The safety profile should be discussed not only in relation to best supportive care but also in relation to the overall safety population.
6. The findings of hypertension, hypomagnesaemia and hypokalaemia in the defibrotide group among subjects with pre-existing renal insufficiency should be discussed in more detail, also in relation to the overall safety population.
7. For participants with pre-existing intrinsic lung disease at baseline in study 15-007, the MAH is asked to discuss the safety findings in relation to the overall safety population.

SmPC

8. See attached SmPC with comments.

14. Assessment of the responses to the 2nd request for supplementary information

14.1. Major objections

Clinical aspects

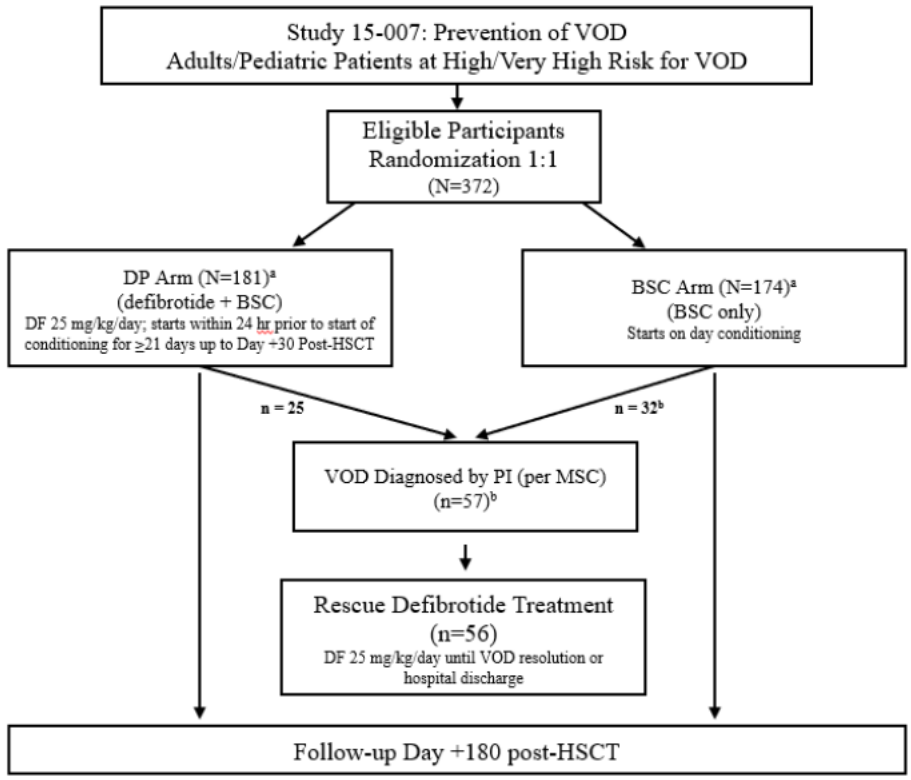
Safety

Question 1. The numerical imbalance in study 15-007 on mortality both during the prophylaxis phase, with a higher mortality in the defibrotide group as compared to best supportive care, as well as during the rescue phase, especially among those initially randomised to defibrotide, should be further addressed. These data are in line with previous prophylaxis data indicating increased mortality with defibrotide, particularly in the paediatric population. The response should include the following:
a. The survival data separated by subjects diagnosed with VOD during study 15-007 who received defibrotide and those diagnosed with VOD who did not receive defibrotide. Any difference should be discussed, including any differences in clinical findings between these groups that could be of relevance.
b. A discussion on the findings of higher mortality in the rescue phase among those initially randomised to defibrotide as compared to those initially randomised to best supportive care, including any differences in clinical findings between these groups that could be of relevance.
c. A discussion of the mortality findings during both prophylaxis and treatment of VOD in study 15-007 in relation to the totality of data on mortality based on relevant previous prophylaxis studies and VOD-treatment studies. This should include whether there are any clinical characteristics that could be relevance in relation to mortality risk as well as a separate discussion on paediatric patients.

Summary of the MAH's response

Study 15-007 was designed to collect additional data to support the safety of defibrotide in a randomized multicenter clinical trial. The study was a phase 3 clinical study using an adaptive design comparing the efficacy and safety of defibrotide prophylaxis (DP) in addition to best supportive care (BSC) versus BSC alone in the prevention of hepatic VOD in adult and pediatric participants undergoing HSCT who were at high risk or at very high risk of developing VOD. The study was not designed to assess or compare the efficacy and safety of defibrotide treatment of VOD during the rescue phase of the study. A total of 372 participants were randomized and included in the final analysis of the study, which was in line with the originally anticipated study sample size. A schematic diagram of study 15-007 design is presented in Figure 1.

Figure 1: Schematic of Study 15-007 Design



[a]Number of participants who received at least 1 dose of study treatment.
[b]One participant (Participant ID: 8108-1002) diagnosed with VOD but withdrew from study on the day of VOD diagnosis, hence didn't receive defibrotide rescue treatment

All participants in either arm of the study who were diagnosed with VOD based on Principal Investigator (PI) assessment received defibrotide 25 mg/kg/day as rescue treatment.

The prophylaxis phase of the study started on the baseline date and ended on the date of study completion/early termination. If VOD occurred, the prophylaxis phase started on the baseline date and ended on the day before the start date of rescue defibrotide (ie, rescue treatment start date minus 1). The rescue phase was defined as the start date of rescue defibrotide treatment and ended on the date of study completion/early termination.

The MAH has performed an in-depth investigation of the study data and found that mortality results are in fact not imbalanced, but similar, for participants by the randomized treatment arms. After investigating the safety data in great detail, the MAH concludes that there was no imbalance in mortality between the 2 study arms, no new safety signals for defibrotide have been observed in this

study and that the safety results are comparable between the 2 arms in both phases (prophylaxis and rescue) of the study. Safety data from Study 15-007 are consistent with the known safety profile of defibrotide. The MAH will illustrate the following foundational points related to the design and analyses of Study 15-007 and highlight several factors that have contributed to the observed results presented in the Study 15-007 final CSR.

•Randomization to DP arm versus BSC arm only occurred once – at the start of the prophylaxis phase. Results from the study prophylaxis phase provide interpretable comparisons and are presented in response to Question (Q)1c. Study 15-007 was not designed to evaluate defibrotide for the treatment of VOD, which would have required randomization to defibrotide or comparator to occur after VOD diagnosis with or without preceding prophylaxis. Doing so would enable evaluation of treatment efficacy between the 2 treatment arms; however, in the absence of this, there is no reliable comparison for treated vs untreated VOD events as it would be confounded by the clinician's diagnosis of VOD, since all participants (except one participant who withdrew at VOD diagnosis) determined to have VOD by the treating physician (ie, Principal Investigator [PI]) were given defibrotide as rescue treatment. Therefore, any group/s resulting post-randomization are not valid comparators and violate the principle of randomization.

•Per study protocol and final Statistical Analysis Plan (SAP), the primary and key secondary endpoints of the study were based on an independent Endpoint Adjudication Committee (EPAC) assessment of VOD diagnosis. Both EPAC and PIs used the Modified Seattle Criteria (MSC) in their assessment of VOD diagnosis. However, the following are important differences:

−The diagnosis of VOD, based on the MSC criteria (a highly sensitive and less specific criteria [McDonald, 1993]), requires real-time clinical judgement, close monitoring of patients with a multidisciplinary team approach to ensure correct diagnosis and management. EPAC assessment of VOD was performed using treatment-blinded, electronic review of participants' data; the assessment was performed remotely and retrospectively.

−VOD events identified by the EPAC for the most part are not the same as VOD events identified by the PI, who deemed defibrotide rescue treatment necessary hence, more severe VOD. Any comparison during the rescue phase between defibrotide-treated VOD (specifically, VOD diagnosed by both PI and EPAC) and EPAC-only identified VOD, yet untreated with defibrotide, is confounded because cases identified by EPAC only would be either incorrect or so mild as to not require treatment with defibrotide according to the assessment of the PI and the multidisciplinary clinical care team.

−Survival of participants who were diagnosed with VOD by PI and treated with defibrotide rescue treatment is consistent with efficacy data of defibrotide from previous studies (Richardson, 2019; Richardson, 2016). A retrospective review by the MAH of data from EPAC adjudication indicates that participants diagnosed with VOD by EPAC only (ie, not by PI), and who therefore did not receive defibrotide rescue treatment, had not experienced clinical VOD (refer to Q1a andQ1c) hence, do not make a valid comparator group for those who received defibrotide rescue treatment.

Based on the Agency request, the MAH has performed the requested analyses, and further details are provided on the differences in survival analyzed by VOD diagnosis and defibrotide rescue treatment (Q1a), as well as mortality during the rescue phase by randomized groups (Q1b) with an assessment of relevant clinical findings. Furthermore, the MAH provides a detailed discussion on the overall mortality findings during both phases of the Study 15-007 (prophylaxis phase and rescue treatment phase) in context with all previously-completed VOD-prophylaxis and VOD-treatment studies evaluating defibrotide, including an additional discussion with respect to pediatric patients (Q1c).

References

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MAH response to 1a, survival data:

In Study 15-007, an Endpoint Adjudication Committee (EPAC) was set up to provide independent, blinded, medical review and adjudication of VOD diagnosis for the analyses of the primary and key secondary efficacy endpoints in the study. EPAC-assessed VOD diagnosis was based on the Modified Seattle Criteria (MSC), per study protocol, and was conducted from electronic review of participants' data, remotely and retrospectively. EPAC assessment of VOD did not dictate or influence whether the participant received defibrotide rescue treatment. Only participants with Principal Investigator (PI)-assessed VOD were administered defibrotide rescue treatment as is the case in everyday clinical practice.

Per the Agency's request, additional analysis on survival data is provided for participants diagnosed with VOD by EPAC who then received defibrotide rescue treatment (thus were also diagnosed with VOD by the PI) versus those diagnosed with VOD by EPAC only who did not receive defibrotide treatment (as they were not diagnosed with VOD by the PI).

Based on the revised concordance analysis by Day +100 post-HSCT, a total of 104 participants were diagnosed with VOD based on EPAC-assessment (please refer to Q2). A total of 57 participants were diagnosed with VOD by the PI; however, one participant (Participant ID 8108-1002) was withdrawn on the day of VOD diagnosis and did not receive defibrotide rescue treatment (shown in Table 3).

A total of 44 participants had VOD diagnosed both by EPAC and PI, all of whom received defibrotide rescue treatment, with the exception of 1 participant (Participant ID 8108-1002) who was withdrawn from the study on the date of VOD diagnosis by PI. In cases where the PI did not diagnose VOD by Day +100 post-HSCT (n=60), none of the participants were administered defibrotide rescue treatment as per the study design. The 1 participant mentioned above, who withdrew from the study, is included in the 61 participants in Table 1 since defibrotide rescue treatment was not administered despite the VOD being diagnosed by both EPAC and PI.

Table 1 presents the survival analysis for participants diagnosed with VOD by EPAC and by administration of defibrotide rescue treatment (yes or no).

Table 1: Overall Survival for Participants with EPAC-Assessed VOD by Defibrotide Rescue Treatment (Yes/No) (Study 15-007; ITT Analysis Set)

Subgroup – Receiving Defibrotide as Rescue Treatment or Not Variable, Statistic	Participants with EPAC-Assessed VOD through Day +100 post-HSCT[a]
Participants who Received Defibrotide as Rescue Treatment[b,c]	43
Death, n (%)	23 (53.5)
Censored, n (%)	20 (46.5)
Censored at the End of Study	13 (65.0)
Censored at Early Termination	7 (35.0)
KM Estimate of Median Survival Time in Days (95% CI)	110.0 (57.0, NE)
Participants who did not Receive Defibrotide as Rescue Treatment[b,,c]	61
Death, n (%)	11 (18.0)
Censored, n (%)	50 (82.0)
Censored at the End of Study	41 (82.0)
Censored at Early Termination	9 (18.0)
KM Estimate of Median Survival Time in Days (95% CI)	NE

Abbreviations: CI=confidence interval; EPAC=Endpoint Adjudication Committee; HSCT=hematopoietic stem cell transplant; ITT=intent-to-treat; KM=Kaplan-Meier; NE=not estimable; VOD=veno-occlusive disease.

[a] EPAC assessment of VOD was through Day +100 post-HSCT but the overall survival analysis is to the end of study.

[b] n=the number of participants with EPAC-assessed VOD through Day +100 post-HSCT by defibrotide rescue treatment from the ITT Analysis Set

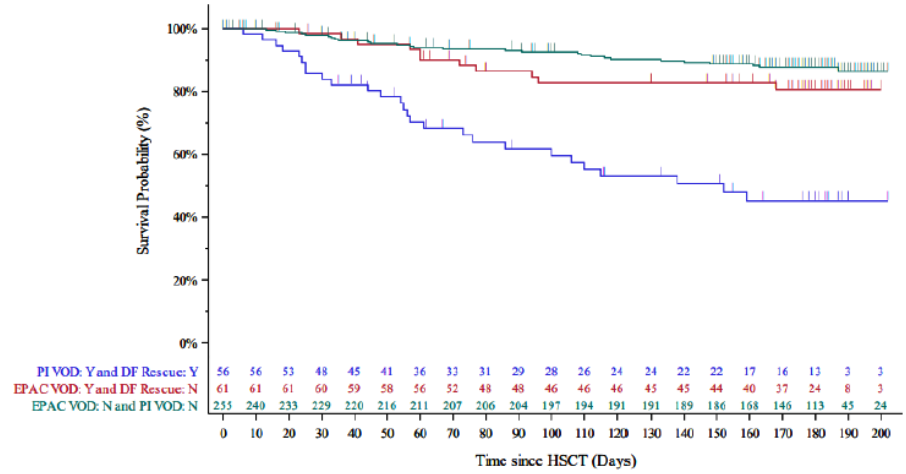
[,c] Subject 8105-1003 was diagnosed with VOD by investigator, treated with Defibrotide rescue treatment, and stopped Defibrotide rescue treatment prior to the date of EPAC-assessed VOD. This subject was included in the analysis in this section.

Source: Table 14.2.6.1.2a

As per Table 1, the participants who were diagnosed with VOD by both EPAC and PI and who therefore received defibrotide rescue treatment had worse survival than participants diagnosed with VOD by EPAC only. Of the participants diagnosed by both EPAC and PI, 23 (53.5%) died. In this subgroup, the median survival was 110 days from the date of HSCT (95% confidence interval [CI]: 57.0, not estimable [NE]). For participants with VOD diagnoses by both EPAC and PI, the survival rate by Day +100 post-HSCT was 54.7% (95% CI: 37.9%, 68.8%) (Table 14.2.6.1.7b), which is consistent with published evidence on efficacy of defibrotide on survival in patients diagnosed with VOD (Richardson, 2016; Richardson 2019).

On the other hand, of the participants diagnosed with VOD by EPAC only, who did not receive defibrotide rescue therapy, 11 (18.0%) died. In this subgroup, the median survival was not reached. Importantly, survival in this subgroup, the estimated survival rate at Day +100 post-HSCT (n=61; 82.8% [95%CI: 70.3%, 90.4%]), was similar to the estimated survival rate at Day+100 for participants who were not diagnosed with VOD by either PI or EPAC in Study 15-007 (n=255; 92.6% [95%CI: 88.3%, 95.3%];Table 14.2.6.1.7a), and is also consistent with published evidence of the high survival rate observed in patients post-HSCT who are not diagnosed with VOD (Baker, 2003).

Figure 2: Overall Survival through Day +200 post-HSCT by VOD Diagnosis (Study 15-007; ITT Analysis Set)



Source: Figure 1.1

With respect to the Agency's request and analysis presented in Table 1, the MAH will present below that major differences in baseline factors existed between the 2 groups of participants diagnosed with VOD by EPAC (those who were treated and not treated with defibrotide); as well, as the criteria that defined their VOD events. Indeed, a higher survival rate in the group diagnosed with VOD only by EPAC is expected and is consistent with survival in patients who do not develop VOD post-HSCT (Baker, 2003). A detailed review and post hoc analysis of the EPAC assessment of VOD and relevant clinical findings between these 2 groups of participants (VOD treated and not treated with defibrotide rescue) are described below. This survival analysis cannot be interpreted as a sound estimate of the treatment effect of defibrotide for the following reasons:

The data analysis requested by the Agency to compare groups of participants who were diagnosed with VOD by EPAC who received or did not receive defibrotide rescue treatment is not an appropriate or valid comparison. The study was not designed to evaluate defibrotide treatment of VOD. Furthermore, there was no additional randomization following the diagnosis of VOD by the PI. In the absence of this post-VOD randomization, no definitive comparison between treated participants versus untreated participants can be made. The 2 groups of participants (treated and untreated) are defined by disagreement in VOD diagnosis between EPAC (who did not influence treatment of VOD) and the PI (who did dictate treatment of VOD based on their own diagnosis). Upon further review of the EPAC assessment, participants who were diagnosed with VOD only by EPAC (but not by PI) likely did not experience clinical VOD (n=60), and thus, are not a valid comparator group for the additional analysis. VOD cases that were diagnosed by both EPAC and the PI and required defibrotide treatment, as determined by the PI, were at higher risk of developing VOD as shown in Table 2 and had a more severe presentation of VOD. Thus, any comparison between defibrotide-treated VOD (specifically, VOD diagnosed by both PI and EPAC) and EPAC-identified, but untreated VOD, is confounded by the clinical diagnosis of VOD made by the PI and the multidisciplinary treatment team. The 43 participants who had VOD diagnosed by both EPAC and PI represent only a proportion (43/56, 76.8%) of all participants diagnosed with VOD by PI who received defibrotide rescue treatment. Therefore, any analysis based on EPAC diagnosis of VOD and treatment with defibrotide (yes or no) does not include all participants diagnosed with VOD by PI who received defibrotide rescue treatment. The results could be biased and are difficult to interpret correctly. Furthermore, Table 2 presents baseline characteristics that are known risk factors associated with developing VOD post-HSCT (Cairo, 2020; Mohty, 2020) for participants in Study 15-007 with EPAC-assessed VOD who were treated with defibrotide compared with those who were not treated with defibrotide.

All risk factors listed in Table 2, with the exception of matched unrelated transplant, were higher in participants diagnosed with VOD by both EPAC and PI and who therefore received defibrotide (diagnosis agreement) compared to patients with VOD diagnosed by EPAC only who did not receive defibrotide (diagnosis disagreement). This is consistent with the inference that the PI diagnosed the more severe form of VOD while EPAC-only VOD cases were either incorrectly classified or much milder.

Prior use of ozogamicin (gemtuzumab or inotuzumab) is the number one risk factor associated with the development of VOD (> 10-times greater risk) (Cairo, 2020). The prior use of ozogamicin was 13.0% greater for the participants treated with defibrotide rescue treatment. The use of myeloablative conditioning, which may have included busulfan or fludarabine-based regimens), and is associated with a 3- to 10-times greater risk of developing VOD, was another notable difference with a 23.8% greater incidence of use for participants who received defibrotide rescue treatment.

In addition, the incidence of participants who had haploidentical HLA mismatched donor transplants was 21.1% greater in the participants who received defibrotide rescue treatment (ie, diagnosed with VOD by both EPAC and PI) versus did not (ie, diagnosed with VOD by EPAC only).

Taken together, these clinical data illustrate that these 2 groups of participants were not balanced at baseline and participants who ultimately developed VOD as assessed by both PI and EPAC were at a much greater risk, and likely had more severe cases of VOD compared to those diagnosed only by EPAC.

Table 2: Baseline Characteristics Associated with Increased Risk of VOD Following HSCT with a >5% Difference between Groups (Study 15-007; ITT Analysis Set)

Baseline Characteristic, n (%)	Participants who received defibrotide as rescue treatment N=43	Participants who did not receive defibrotide rescue treatment N=61	Between Group Difference (%)
Haploidentical (half-matched)	14 (32.6%)	7 (11.5%)	21.1%
Matched unrelated	10 (23.3%)	25 (41.0%)	-17.7%
Myeloablative conditioning	37 (86.0%)	38 (62.3%)	23.8%
Busulfan conditioning	27 (62.8%)	20 (32.8%)	30.0%
Fludarabine conditioning	20 (67.4%)	32 (52.5%)	15.0%
Prior gemtuzumab or inotuzumab	19 (44.2%)	19 (31.1%)	13.0%
Very High Risk[a]	27 (62.8%)	32 (52.5%)	10.3%
Mean age	25.5 years	20.2 years	5.3 years
Median age	17.0 years	10.0 years	7.0 years

Abbreviations: EPAC=Endpoint Adjudication Committee; HSCT=hematopoietic stem cell transplant; ITT=intent-to-treat; VOD=veno-occlusive disease

[a] For the subcategory under Very High Risk, percentages were calculated with the number of participants with very high risk in each subgroup as the denominator. Categories for very high risk included osteopetrosis and undergoing myeloablative conditioning, primary HLH, Griscelli II Chediak-Higashi Syndrome, prior treatment with an ozogamicin, Class III or High-Risk Thalassemia.

Note: Data include all participants (pediatric and adults) who were diagnosed with VOD by EPAC

Source: Table 14.2.6.1.1

It is clear that diagnosis of VOD requires a holistic view of the patient's condition over time and often involves a multidisciplinary team decision. The PI, within a multidisciplinary team, was closely monitoring the participant's condition daily, and had access to more details of the participant's case history, enabling clinical judgement to provide a differential diagnosis other than VOD and to rule out a diagnosis based on an isolated or transitory elevation in an MSC criterion parameter. In contrast, given the remote and retrospective assessment by EPAC, it is unlikely that all of the relevant clinical factors could be taken into consideration (please see below).

The use of MSC is regarded as a guideline (not an algorithm) for diagnosis but does not guide treatment decisions. MSC is a high-sensitivity, low-specificity tool with a limitation in assessing the severity of VOD (McDonald ,1993). Study 15-007 illustrated some of the challenges with diagnosing VOD in this manner, namely the tendency for EPAC to over-diagnose VOD based on point estimates such as isolated or transient conditions (weight increase, elevated bilirubin, hepatomegaly, and ascites) using MSC as an algorithm in isolation. While the EPAC adjudication process used in this study was a recommended 2+1+1 model, significant discrepancies in their diagnosis of VOD were evident even between the adjudicators themselves. On examining the EPAC activity report, the following were observed:

Note: The adjudication model (2+1) included 3 rounds as follows: Round 1- two EPAC adjudicators reviewed participants' data independently to assess if the participant had VOD. If both adjudicators arrived at the same diagnosis, the adjudication was considered complete. If the two adjudicators were discrepant in their diagnosis, the patient data was reviewed in Round 2 by a 3rd independent adjudicator. If this 3rd adjudicator agreed with either one from round 1 the patient was considered complete in Round 2. If the 3rd adjudicator's diagnosis did not agree with either adjudicator in the first round the patient was adjudicated in a consensus meeting in round 3. (Module 5.3.5.4/JZP15-007 CSR/Section 8.9.7) The majority of participants (67/104 [64.4%]) diagnosed with VOD by EPAC in Study 15-007 required 2 or more rounds of review before a final diagnosis was confirmed due to discrepancy in the diagnosis by the different adjudication members (EPAC Activity Report - spreadsheet available upon request). Of the cases with disagreement in diagnosis by EPAC and PI, approximately one-third of cases were potentially disputed or borderline cases as annotated by the EPAC, in which a differential diagnosis/causal factor (preparative regimen, chemotherapy, pre-existing liver disease, underlying malignancy, or temporary condition – often volume overload from fluid management leading to isolated weight gain) was more likely the cause for meeting an MSC parameter than a true VOD diagnosis. In the cases with agreement in diagnosis by EPAC and PI, very few participants were notated by the EPAC as borderline or potentially disputable, and no cases were given a differential diagnosis. Over half of the cases with disagreement in diagnosis by EPAC and PI relied on a transient or isolated parameter to meet MSC for diagnosis. In many of these cases, 2 criteria led to the diagnosis and an isolated and/or transient increase in weight was the determining factor for EPAC diagnosis. As noted by an EPAC member on many of these cases, the transient increase in weight was likely due to volume overload, which is a common occurrence due to fluid management given as standard of care in this setting, yet the VOD diagnosis was not overturned. Evaluating the details of the MSC criteria used in each case for VOD diagnosis by EPAC and specifically, between the cases with VOD diagnosis by PI ("diagnosis agreement") or no diagnosis by PI ("diagnosis disagreement"), there were notable clinically-meaningful differences observed. In the "diagnosis agreement" cases, 91% involved an elevation of bilirubin; whereas, in the "diagnosis disagreement" cases, only 28% involved an elevation of bilirubin (Module 5.3.5.4/JZP15-007 CSR/ Listing 16.2.7.1 and Listing 16.2.7.2). Based on published evidence, patients with VOD and hyperbilirubinemia have reduced Day +100 post-HSCT survival (54% versus 87%) and a higher incidence of multiple organ dysfunction (MOD; 41% versus 26%) (Corbacioglu, 2020). In one study, anicteric VOD cases (VOD cases without hyperbilirubinemia) were observed in 15% and 29% of adult and pediatric cases, respectively (Corbacioglu 2020). In Study 15-007, 72% of participants with "diagnosis disagreement" cases were anicteric, which is significantly higher than historical evidence, while for the "diagnosis agreement" cases, incidence of anicteric VOD (9% of cases) was more in-line with published literature.

The discrepancies in VOD diagnosis largely explains the difference in survival between the cases where diagnosis of VOD was by EPAC only and therefore, the participants did not receive defibrotide (ie, were unlikely true clinical cases of VOD), and the cases of VOD diagnosed by both EPAC and PI (severe cases of VOD diagnosed also by PI, and therefore, received defibrotide rescue treatment). Since any

comparison between these 2 subgroups of participants is confounded, a high-level comparison between Study 15-007 results and historical data was assessed. The estimated Kaplan-Meier (KM) survival at Day +100 post-HSCT in participants who had VOD diagnosis by both EPAC and PI and who received defibrotide rescue (54.7%; Table 14.2.6.1.7b) is consistent with historical/published Day +100 survival rates from defibrotide treatment studies ranging between 38.2 to 56% (Richardson, 2019; Richardson, 2016).

Since the cases diagnosed by both EPAC and PI did not include all participants who received defibrotide rescue treatment, a survival analysis based on PI assessment of VOD is more appropriate. Table 3 presents the survival analysis for participants diagnosed with VOD based on PI assessment. Overall, of the 56 participants with PI-diagnosed VOD, fewer than half (n=27; 48.2%) died on study. The KM estimated survival rate at Day +100 post-HSCT in the PI diagnosed VOD cases who were treated with defibrotide rescue treatment is 59.6% (95% CI: 44.9%, 71.6%; Table 14.2.6.1.7a), consistent with known efficacy data of defibrotide in treatment VOD (Richardson, 2019; Richardson, 2016).

Table 3: Overall Survival for Participants with Investigator-Diagnosed VOD by Defibrotide Rescue Treatment (Yes/No) (Study 15-007; ITT Analysis Set)

Subgroup – Receiving Defibrotide as Rescue Treatment or Not Variable, Statistic	Participants with Investigator-Diagnosed VOD
Participants who Received Defibrotide as Rescue Treatment[a]	56
Death, n (%)	27 (48.2)
Censored, n (%)	29 (51.8)
KM Estimate of Median Survival Time in Days (95% CI)	152.0 (76.0, NE)
Participants who did not Receive Defibrotide as Rescue Treatment	1
Death, n (%)	0
Censored, n (%)	1 (100)

Subgroup – Receiving Defibrotide as Rescue Treatment or Not Variable, Statistic	Participants with Investigator-Diagnosed VOD
KM Estimate of Median Survival Time in Days (95% CI)	NE

Abbreviations: CI=confidence interval; HSCT=hematopoietic stem cell transplant ; ITT=intent-to-treat ; KM=Kaplan-Meier; NE=not estimable; VOD=veno-occlusive disease.

[a] n=the number of participants with investigator-diagnosed VOD by defibrotide rescue treatment from the ITT Analysis Set

Source: Table 14.2.6.2.2

In summary, the overall survival in participants who developed VOD and received defibrotide rescue treatment is consistent with known survival data on defibrotide from published literature (Richardson, 2019; Richardson, 2016). The survival in participants with VOD diagnosed only by EPAC, and therefore, who did not receive defibrotide rescue treatment, is consistent with the overall survival in patients undergoing HSCT without developing VOD (Baker, 2003). The cumulative results of the analyses presented, which are consistent with the literature, provides strong evidence that the 2 groups of participants with VOD diagnosed by EPAC (treated and not treated with defibrotide) are very different: 1 group who did not experience true clinical VOD and had a better overall prognosis, and another group that had very high risk for developing VOD and developed severe VOD and, hence, required rescue treatment with defibrotide. Thus, no comparison or conclusion can be drawn regarding defibrotide VOD treatment in Study 15-007, which was designed to evaluate defibrotide prophylaxis and not treatment of VOD.

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Assessor's comment:

A clear strength of study 15-007 is the external blinded endpoint adjudication committee (EPAC), that was provided with clinical data to assess whether VOD occurred or not. It is fully agreed that establishing the diagnosis of VOD could be difficult. The limitations with the modified Seattle criteria are also well known. Nevertheless, for this study, both the EPAC and the principal investigators had access to similar clinical data and utilised the same criteria for diagnosis. The argument that 'real-time clinical judgement, close monitoring of patients with a multidisciplinary team approach' could strengthen the diagnostic ability has not been justified by any actual clinical data that were taken into account by investigators but not provided to the EPAC. Thus, the discordance between investigators and the EPAC could be due to underlying bias resulting from investigators being non-blinded to study treatment.

Notably, the authorisation of defibrotide relied on clinical data from one open-label pivotal trial with a historical control group for which VOD was retrospectively assessed. Therefore, the MAH argumentation warrants some caution regarding any lack of robustness of retrospective, remote assessment of VOD.

The overall survival among those who received defibrotide as rescue treatment was clearly higher among those who were diagnosed by the EPAC only (and therefore were not treated with defibrotide); 11/61 or 18% of these subjects died as compared to 23/43 or 53.5% of those who were diagnosed as VOD by both EPAC and investigators (and were therefore treated with defibrotide). The survival at Day +100 post-HSCT among individuals in study 15-007 who did not develop VOD (n = 255) was higher (92.6%) as compared to those who developed VOD as diagnosed by the EPAC only (n = 61, survival 82.8%).

The attempt to present data on risk factors for VOD at baseline is appreciated; some differences are noted between those with a VOD diagnosis by the EPAC and those diagnosed by investigators only. However, several well recognised risk factors were not included among the presented data, such as (degree of) liver disease, pulmonary function and underlying disease (ie cause of HSCT). Unrelated donors appear more frequent among those diagnosed by the EPAC only, whereas myeloablative conditioning was more frequent among those who received defibrotide as rescue treatment (including busulfan and fludarabine conditioning). More than half of patients in both these groups had a 'very high risk' of VOD, 27/43 or 62.8% among those diagnosed by investigators and 32/61 or 52.5% of those diagnosed by the EPAC. Nevertheless, the relevance of these data to support whether subjects actually developed VOD or not are unclear.

The extensive argumentation on why EPAC-diagnosed subjects with VOD actually did not actually have VOD is noted; notably, this could question the entire study design given that the primary endpoint was EPAC-adjudicated VOD. It is argued that among EPAC-adjudicated cases of VOD, a differential diagnosis or causal factor was often more likely than actual VOD, examples including preparative regimen, chemotherapy, pre-existing liver disease, underlying malignancy, or temporary condition such as volume overload. However, these factors are well known risk factors and/or symptoms of VOD and thus, the argumentation is somewhat difficult to follow. The only clinical factor that is described to differ between subjects diagnosed as VOD by both investigators and the EPAC, and those diagnosed by the EPAC only, is elevation of bilirubin; notably, however, subjects diagnosed only by investigators were older (median age 17 years; Table 1 above) than EPAC-diagnosed subjects (median age 10 years); anicteric VOD is well known to be more frequent among paediatric patients.

A comparison between survival in EPAC-diagnosed VOD and patients post-HSCT without VOD in a publication from 2003 is not considered valuable, given that EPAC-diagnosed subjects were indeed considered to have VOC by the EPAC and that there are considerable differences in treatment regimens used for conditioning as well as regarding the populations eligible for HSCT between contemporary care as compared to older data.

MAH response to 1b, mortality data:

All, except one, participants who were diagnosed by the PI with VOD in both randomized treatment arms of the study (defibrotide prophylaxis [DP] and best supportive care [BSC]) received defibrotide rescue treatment. One participant, in the BSC arm withdrew from the study on the date of VOD diagnosis and did not receive defibrotide rescue treatment (Participant ID 8108-1002). As noted by the Agency and acknowledged in the background section above, a seemingly higher mortality rate was observed in participants who were randomized to the DP arm versus those randomized to the BSC arm, as reported in the final CSR for non-relapse mortality (NRM) and TEAEs leading to death in the rescue phase (Module 5.3.5.4/JZP15-007 CSR/Section 5.1.2.4 and Section 5.2.1.4). Contributing factors for the observed imbalance are as follows:

• Per the study electronic case report form (eCRF) completion guidelines, detailed reporting on the cause of death was not mandatory.

• The definition of NRM used in the final analysis of the study (Module 5.5.3.4/JZP 15-007 CSR/Section 3.7.1) did not include non-malignant relapse/disease progression. This introduced a biased estimate of NRM.

• Not all causes of death were reported as adverse events (AEs) or were considered treatment emergent; for example, not all cases of VOD were reported as a TEAE since VOD was an endpoint in the study.

The MAH has now investigated all causes of death that were reported on all relevant eCRFs, including Grade 5 (fatal) AEs and pharmacovigilance reporting (captured in the MAH safety database) and has prepared an additional listing of all deaths (any cause) post-hematopoietic stem cell transplant in the rescue phase of the study (HSCT) (Listing 1.2a). Individual participant narratives describing all deaths are provided in Module 5.3.5.4/JZP15-007 CSR/Section 11.

Per the Agency's request, an additional analysis was completed to provide incidence of death, for participants with PI-diagnosed VOD who received defibrotide rescue treatment, by randomized treatment arm (ie, randomized prior to the prophylaxis phase) and by age group (Table 4). However, please note that treatment arms/groups defined by post-randomization occurrence of VOD are not randomized groups, and hence, may not be comparable with respect to baseline prognostic characteristics nor in the severity of VOD (please refer to Q1a).

In total, 27 participants died during the rescue phase of the study. Of the 27 deaths, the number of participants who died by the randomized treatment arm is similar: 14 deaths among those randomized to the DP arm and 13 deaths among those randomized to BSC arm.

Per the safety analysis of fatal TEAEs presented in the CSR, during the rescue phase, 12 participants in the DP arm and 8 participants in the BSC arm experienced at least 1 TEAE leading to death (Module 5.3.5.4/JZP15-007 CSR/Table 16). However, as shown in Table 4 and Listing 1.2a, there were additional deaths compared to the summary of TEAEs leading to death in the CSR final analysis. These fatal TEAEs were not included in the final analysis, as the fatal events were outside the study reporting

period. This has resulted in the imbalance observed in the final CSR while, in fact, there were no differences in the number of deaths between the treatment arms in the study.

Table 4: Summary of Death for Participants with Investigator-Diagnosed VOD who Received Defibrotide Rescue Treatment by Treatment Arm and Age Group. (Study 15-007; Safety Analysis Set)

Age Group Variable, Statistic	DP Arm N=181	BSC Arm N=174
Overall number of Participants[a], n	25	31
Death, n	14	13
Censored, n	11	18
Number of Pediatric Participants (<=16 years), n	15	15
Death, n	7	5
Censored, n	8	10
Number of Adult Participants (>16 years), n	10	16
Death, n	7	8
Censored, n	3	8

Abbreviations: BSC=Best Supportive Care; DP=defibrotide prophylaxis; VOD=Veno-occlusive Disease
[a] n = the number of participants with investigator-diagnosed VOD who received defibrotide rescue treatment by treatment arm and age group from the ITT Analysis Set
Source Table 14.2.6.2.3a

Among the 12 pediatric participants in the rescue phase who died, 7 participants were in the DP arm and 5 participants in the BSC. However an equal number of pediatric participants by treatment arm died due to TEAEs: n=5, DP arm and n=5, BSC arm (Listing 1.2a). The additional 2 participants in the DP arm who died during the rescue phase both died due to disease progression/disease relapse.

In the rescue phase, causes of death among the 5 pediatric participants who died due to TEAEs in the DP arm were: cardiac arrest (n=1), multiple organ failure (MOF) and VOD (n=1), pseudomonal sepsis (n=1), MOF and candida sepsis (n=1), and intracranial haemorrhage (n=1) (Listing 1.2a). Of these, the TEAE of intracranial haemorrhage was the only TEAE leading to death reported by the PI as related to defibrotide treatment (Module 5.3.5.4/JZP15-007 CSR/Listing 16.2.10.5). This participant (Patient ID 1603-1004), with the intracranial hemorrhage had acute lymphoblastic leukemia (ALL) with severe thrombocytopenia prior to VOD diagnosis and the start of defibrotide rescue treatment; in addition, this participant was receiving heparin as a concomitant medication. These factors are all associated with increased risk of bleeding.

In the rescue phase, causes of death among the 5 pediatric participants in the BSC arm were: brain death (n=1), respiratory failure (n=1), chronic respiratory failure/ microangiopathy/ pulmonary haemorrhage (n=1), adenoviral infection (n=1) and sepsis (n=1).

Of the 15 adult participants who died in the rescue phase in the study, a similar number of participants were randomized to the DP arm (n=7) and the BSC arm (n=8) (Table 4). For the adult participants in the DP arm who died, causes of death were reported as infection (sepsis; n=4) – one of whom also had VOD, VOD was given as cause of death for 2 additional participants, and 1 participant died of leukoencephalopathy. Causes of death among adult participants in the BSC arm were similar to those in the DP arm: VOD (n=2), sepsis (n=1), pneumonia (n=2), device infection (n=1), MOF (n=1) and respiratory failure (n=1).

Relevant clinical findings: The following clinical findings for participants in the DP arm who died in the rescue phase compared to the participants in BSC arm who died in the rescue phase are of relevance as these are known poor prognostic factors associated with poor outcome and increased mortality

(Listing 1.4). Despite this difference, a similar number of participants died in either treatment arm of the study:

· Participants in the DP arm who died had more recurrent disease (≥ 2 recurrence, n = 8), indicating refractory/resistant disease versus participants in the BSC arm (≥ 2 recurrence, n = 2)

• The 2 participants in the DP arm who had disease progression/disease relapse had associated risks including participant age, primary diseases, and Asian race, which are recognized as high risk for recurrence and poor outcome (Carreras, 2019): Participant ID 3905-1007, a 2-year-old with advanced stage neuroblastoma; Participant ID 6102-1008, a 4-year-old Asian with familial hemophagocytic lymphohistiocytosis (HLH).

• A higher number of graft manipulation and T-cell depletion among participants who died in the DP arm (n=6) versus those in the BSC arm (n=2). T-cell depletion is associated with primary disease relapse (Carreras, 2019).

• Delay in defibrotide administration. One pediatric participant in each treatment arm had a primary disease of osteopetrosis. However, the participant in the DP arm was less than 1 month of age at study entry, and defibrotide administration was delayed until the participant became eligible (> 1 month). Delay in defibrotide administration combined with participant age is considered likely to have contributed to the adverse outcome in this participant (Richardson, 2017; Carreras, 2019; Parikh 2019).

Overall, a similar number of participants died during the rescue phase of the study regardless of randomized treatment arm (ie, randomized prior to the prophylaxis phase) and regardless of age subgroup. An equal number of pediatric participants died in each treatment arm due to non-relapse causes. Two pediatric participants in the DP arm died due to relapse/progression of primary disease. A similar number of adult participants died during the rescue phase due to NRM, regardless of randomized treatment arm. Given the evidence above, there is no increase in mortality reported in the DP arm compared with the BSC arm in the rescue phase and causes of death are similar for both treatment arms. In Study 15-007, mortality rates reflect those anticipated in this patient population undergoing HSCT (Richardson, 2016; Styczyński, 2019).

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Assessor's comment:

Non-relapse mortality was a secondary endpoint of study 15-007 and was defined as death that occurs after HSCT in participants who were noted as having malignant primary disease on the disease history eCRF and who did not have primary disease relapse post-HSCT. Only participants with malignant primary disease at baseline were included in the analysis. As discussed in previous rounds, some caution is warranted given that the primary endpoint was not met; however, a cause of concern was the numerical imbalance in non-relapse mortality between participants in the defibrotide arm and the best supportive care arm. Of the participants with malignant primary disease history, 22 of 147 participants (15.0%) in the DP arm and 11 of 139 participants (7.9%) in the BSC arm experienced NRM by Day +100 post-HSCT. Of the participants with malignant primary disease history, 25 of 147 participants (17.0%) in the DP arm and 16 of 139 participants (11.5%) in the BSC arm experienced NRM by Day +180 post-HSCT.

Although it is reassuring that there was no difference in overall mortality between initial (randomised) treatment groups during the 'rescue phase', the discussion on prevalence of risk factors for poor prognosis among those who actually died is of little relevance; rather, a discussion on risk factors for poor outcome for the respective entire treatment groups could have been of value. The clear numerical difference in non-relapse mortality between patients initially randomised to defibrotide as compared to those initially randomised to best supportive care is considered to further substantiates that the benefit-risk of defibrotide for prophylaxis of VOD is negative.

MAH response to 1c, mortality during prophylaxis and treatment of VOD:

In the final study analysis of Study 15-007, a seemingly higher mortality rate was observed in participants who were randomized to the DP arm versus those randomized to the BSC arm (randomization was prior to the prophylaxis phase) — data that were reported in the final CSR for non-relapse mortality (NRM) and treatment-emergent adverse events (TEAEs) leading to death in the rescue phase (Module 5.3.5.4/JZP15-007 CSR/Section 5.1.2.4 and Section 5.2.1.4). The MAH has performed an in-depth investigation of the study data, as was described in the responses to major objection Q1a and Q1b and substantiated that mortality results for participants by the randomized treatment arms are, in fact, comparable.

By investigating the safety data in greater detail, the MAH concludes that no new safety signal was observed in this study with the safety results being comparable between the study treatment arms. Safety data from Study 15-007 are consistent with the known refence safety information of defibrotide. The MAH highlights that several factors have contributed to a misrepresentation of data leading to a numerical mortality imbalance presented in the final CSR.

• Study 15-007 was powered to detect a difference in prevention of VOD with DP in addition to BSC compared to BSC alone; it was not designed to detect a difference between treatment arms in the treatment of VOD during the rescue phase.

• The definition of NRM used in the final analysis of the study (Module 5.5.3.4/JZP15-007 CSR/Section 3.7.1) did not include non-malignant relapse/disease progression. This introduced a biased estimate of NRM (refer to Q1b and see below).

• The final analyses of the study were based on specific fields in the eCRF with limited allowance for cross-form capturing of data. This has resulted in unforeseen incomplete or missing follow-up data in the final analysis, despite the data being available via other study capturing methods (eg, VOD resolution, disease relapse, and fatal events/causes of death).

• Randomization to the DP arm versus BSC arm occurred once – at the start of the prophylaxis phase. Results from this study phase provide interpretable comparisons and are presented below. Therefore, any subgroups that resulted post-VOD diagnosis in the rescue phase (ie, post-randomization) are not valid comparators and violate the principle of randomization.

The MAH reviewed the study data in more detail, including additional analyses presented in the responses to Q1a and Q1b, and concluded that the safety results from Study 15-007 are similar between the randomized treatment arms. No new safety signals are observed, and the results are consistent with the known safety profile of defibrotide. This conclusion is consistent with that of the independent study Data Monitoring Committee (DMC) who reviewed the safety data at regular intervals (every 6 months), including at the interim and the final analysis of the study. While utilization of a central blinded adjudication for study efficacy endpoints is generally preferred versus treating physician/Principal Investigator (PI) assessment to alleviate potential bias, the method used and misalignment between the local and central assessment highly impact interpretation of the results. The study was designed with best knowledge at the time and following recommendations, but in retrospect, a deep evaluation of the study data have highlighted the consequences for how the study was conducted and ultimately analyzed. Further, this underscores the complexity around VOD diagnosis and therapy. Available evidence on central adjudication versus local PI assessment has shown high variability and has largely been dependent on the methods used, parameters used for adjudication, design of the study, and the clinical endpoints (Ford, 2016).

Modified Seattle Criteria (MSC) was used in Study 15-007 for VOD assessment by both the EPAC and the PI. MSC is highly sensitive but has low specificity (Volin, 2016) and has high limitations in assessing severity of VOD, for which defibrotide is approved. EPAC VOD assessment was conducted from electronic review of participants' data, remotely (outside the clinic) and in a retrospective manner (ie, not "real time"), while the PI had the advantage of close and continuous monitoring of participants in real time and with participants whom they likely had a clinical history. The decision to administer defibrotide rescue treatment was at the discretion of the PI, as was the assessment of VOD resolution, and management of TEAEs. EPAC had no influence on defibrotide rescue treatment nor on the assessment of VOD resolution.

Furthermore, VOD diagnosis has been shown to be best addressed by a multidisciplinary approach and is highly-dependent on expert clinical judgement given the variable differential diagnosis of post-transplant complications sharing similar non-specific clinical signs and symptoms (Volin, 2016). In examining the adjudication process, while a model of 2+1 (a recommended process [Ford, 2016]), was used in this study, there appears to be significant discrepancies between the adjudicators in their diagnosis of VOD (described in the response to Q1a). This resulted in several rounds of adjudication for a significant number of participants. In addition, the criteria that EPAC reported in their final diagnoses appear to have been based solely on the 4 criteria from MSC (bilirubin, weight, hepatomegaly and ascites), with the majority of diagnoses being based on hepatomegaly and ascites or weight (see Q1a). EPAC provided no description or discussion with respect to baseline characteristics (eg, primary disease, age, race) or other clinical conditions, which may have been risk factors of the participants and/or indicate potential diagnosis other than VOD.

Given the substantive discrepancy between PI and EPAC diagnosis of VOD (refer to response Q2), analyses based on EPAC assessment of VOD likely provide distorted results. The participant subgroups derived from EPAC assessment of VOD (those treated or not treated with defibrotide) are not appropriate nor valid for comparison. After careful evaluation of the study data, the MAH would like to highlight that participants diagnosed with VOD by EPAC only and who did not receive defibrotide rescue treatment are highly unlikely to have experienced clinical VOD (please refer to Q1a). Indeed, the following evidence indicate that EPAC-only VOD diagnosis not treated with defibrotide rescue are

unlikely true VOD: The criteria EPAC used in substantiating the VOD diagnosis in these participants; the difference in major baseline prognostic factors presented in Q1a/Table 2; the similar survival rate at Day +100 post-HSCT for the subgroup diagnosed with VOD by EPAC only and not treated with defibrotide with the subgroup of participants not diagnosed with VOD and survival in non-VOD patients from published literature (Baker, 2003) strongly indicate that this subgroup diagnosed with VOD by EPAC only were likely not true clinical VOD. Given the above, it is clear that using EPAC diagnosis of VOD was not optimal for the primary endpoint in the design of study 15-007.

The final analysis of Study 15-007, based on a total of 372 randomized participants (pediatric n=198, adults n=174), showed that the safety data between the 2 treatment arms (DP arm and BSC arm) of the study were similar (Module 5.3.5.4/JZP15-007 CSR/Section 5.2). Overall, there were 65 deaths by the end of the study (Day +180 post-HSCT) (Module 5.3.5.4/JZP15-007 CSR/Table 19): DP arm, n=35 and BSC arm, n=30.

Mortality in the rescue phase, as presented in response to Q1b, was similar between the 2 treatment arms: for the overall safety population (DP arm, n=14 versus BSC arm, n=13), as well as in both pediatric (DP arm, n=7 and BSC arm, n=5) and adult participants (DP arm, n=7 and BSC arm, n=8) (Table 4). In fact, an equal number of pediatric participants died in the DP arm (n=5) versus BSC arm (n=5) during the rescue phase due to causes other than relapse/disease progression. The 2 additional deaths in the DP arm were due to primary disease relapse (Q1b) and had not been highlighted as such in the final analyses, hence resulted in a seeming imbalance in the NRM (Module 5.3.5.4/JZP15-007 CSR/Section 5.1.2.4) and the TEAEs leading to death (Module 5.3.5.4/JZP15-007 CSR/Table 16). Primary disease relapse is a common finding in both clinical practice and published studies as a cause of death early post-transplantation (Styczyński, 2020). Fatal TEAEs assessed by the PI as related to defibrotide were reported in 2 participants, both during the rescue phase of the study (DP arm, n=1 [intracranial hemorrhage] and BCS arm, n=1 [VOD]) (Module 5.3.5.4/JZP15-007 CSR/Section 5.2.1.4).

Similarly, mortality in the prophylaxis phase *(NB up to Day +180 post-HSCT for those who did not develop investigator-diagnosed VOD, Assessor's comment)* of the study (total n=38) was similar between the randomized treatment arms: DP arm, n=21 and BSC arm, n=17 (Listing 1.3a). Of these, 15/38 were due to primary disease relapse: DP arm, n=8 and BSC arm, n=7. In the prophylaxis phase of Study 15-007, of the participants with NRM (23/38 [DP arm, n=13; BSC arm, n=10]), 4 pediatric participants in the DP arm died compared to 4 pediatric participants in the BSC arm. Therefore, the slight imbalance in mortality observed within the prophylaxis phase of the study is with respect to the adult participants (DP arm, n=9; BSC arm, n=7). Causes of mortality are provided in the listing on causes of death during the prophylaxis phase provided for this response submission (Listings 1.3a). Causes of death were consistent with transplant-related TEAEs that are commonly reported for patients undergoing transplant (Styczyński, 2020).

Indeed, based on the detailed information provided above and in Q1b, combining the mortality in the prophylaxis and the rescue phase in Study 15-007, NMR was similar between the randomized treatment arms: DP arm, n=25 and BSC arm, n=23. Therefore, no imbalance in mortality is observed in Study 15-007 for either the prophylaxis and rescue phases of the study, nor for pediatric or adult participants.

As presented in response to Q1a, the estimated survival at Day +100 post-HSCT of 54.7% (in cases diagnosed with VOD by both EPAC and PI who received defibrotide rescue treatment) and 59.6% based on PI VOD assessment (all of whom received defibrotide rescue treatment) (Table 14.2.6.1.7a) are consistent with the known survival rates following defibrotide treatment of VOD reported in previous studies during the clinical development program of defibrotide (Richardson, 2016; Kernan, 2018; Richardson 2010), and real-world data from post marketing registries (Module 5.3.6/EBMT

Registry CSR, Module 5.3.5.4/CIBMTR 2021 CSR, and Module 5.3.5.2/DEFIFrance CSR). As expected, in study 15-007, the estimated survival at Day +100 Post HSCT was noticeably higher in the non-VOD subgroup of participants (no VOD diagnosis by EPAC nor PI) and was similar to the Day +100 post HSCT survival in the subgroup diagnosed with VOD by EPAC (who did not receive defibrotide rescue treatment) and HSCT patients who develop no VOD in published literature. This strongly suggest that EPAC-only VOD diagnosis does not represent a true clinical VOD. Therefore, the requested survival comparison of participants in this study who developed VOD (EPAC assessment) and who received and did not receive defibrotide rescue treatment is neither statistically nor clinically valid. These groups were not randomized and have only resulted due to differences in VOD diagnosis between EPAC and PI. As described in Q1a, there are substantial differences in prognostic characteristics and VOD events; the 2 groups are not appropriate comparators. Furthermore, the high disagreement among the EPAC adjudicators, the multiple rounds of assessment, and the criteria on which VOD was diagnosed, in addition to the substantial differences in clinically-relevant VOD risk factors observed (Q1a/Table 2) between the EPAC-only VOD diagnoses and the PI diagnosed VOD are all indicative that VOD diagnosed by EPAC only who did not receive defibrotide rescue are not true clinical VODs, or at most mild VODs that did not require defibrotide rescue treatment based on the PI judgment. As such, the EPAC-only VOD group is not a valid comparator for survival analysis as requested by the agency.

Several studies have previously shown the benefit of defibrotide in prophylaxis of VOD versus standard of care (Corbacioglu, 2012; Chalandon, 2004; Zhang, 2012). The largest study, the pediatric prophylaxis Study 2004 (Corbacioglu 2012) was the basis for Study 15-007. Study 2004 was a phase 3, multicenter randomized study for prevention of VOD using defibrotide versus standard of care (control) in high-risk pediatric patients undergoing HSCT (Module 5.3.5.1/Study 2004 CSR). The study was conducted in 28 European study centers and included 356 participants (Safety Analysis Set N=353: DP arm, n=177, control arm, n=176). In Study 2004, overall, 32 (18%) participants in the defibrotide prophylaxis (DP) arm, and 29 (16%) participants in the control arm had an AE leading to death. Of these, 24 participants in each arm (DP arm, 13% and control arm, 14%) died before day +180 (Module 5.3.5.1/Study 2004 CSR/Section 12.3.1.1). For all 48 participants (24 in each arm), causes of death included Neoplasms, Malignant and Unspecified (7% and 8% of participants died due to recurrent malignancy, respectively); Infections and Infestations (3% and 6% of participants died due to sepsis or infection, respectively). One death due to gastrointestinal haemorrhage was reported for each treatment arm (possibly related to defibrotide for Participant LZ01SEP2004F285 randomized to DP arm; not related for Participant GF27MAY2001M285 randomized to the control arm without having received defibrotide). In addition, Participant LZ01SEP2004F285 in the DP arm who experienced gastrointestinal haemorrhage, also experienced 2 additional unrelated AEs with outcome of death, including candida sepsis and liver disease. All participants in Study 2004 who developed VOD, regardless of treatment arm, received defibrotide treatment per study protocol. During the VOD treatment phase, 5/24 (21%) participants in the DP arm and 11/36 (31%) participants in the control arm experienced at least 1 TEAE with an outcome of death (Module 5.3.5.1/Study 2004/Table 36). In the DP arm, 1 participant died of disease progression, multiorgan failure (n=2), cardiac arrest (n=1) and idiopathic pneumonia syndrome (n=1). In the control arm, fatal TEAEs in more than 1 participant during VOD treatment with defibrotide included sepsis (n=3), multiorgan failure (n=2), disease progression (n=2), respiratory failure (n=1), and veno-occlusive liver disease (n=1), and hepatobiliary disease (n=2). Given the above, the 2 treatment arms in Study 2004 were generally similar with respect to AEs leading to death. Only 1 participant randomized to the DP arm reported a drug-related serious adverse event (SAE) while receiving defibrotide for prophylaxis (gastrointestinal haemorrhage occurring in a participant with multiple other co-existing SAE/AEs leading to death). A similar AE (gastrointestinal haemorrhage leading to death was experienced by a participant in the control arm without receiving defibrotide prophylaxis or rescue treatment. In summary, study 15-007 data and data from Study 2004 do not support a detrimental effect of defibrotide on mortality.

A number of adult patients have been included in previous studies evaluating the efficacy of defibrotide in prevention of VOD in pediatric and adult patients (Chalandon 2004, Zhang 2012). No safety concerns with respect to defibrotide or increase in mortality have been reported in any of these studies. A more recent pooled analysis was conducted using 10 studies, totaling >1000 participants, that evaluated defibrotide for VOD prophylaxis (Corbacioglu 2020). In this meta-analysis, the overall VOD/SOS incidence following administration of defibrotide was 5% (5% in adults and 8% in pediatric patients). Of the 10 studies, 8 studies evaluated IV defibrotide prophylaxis versus controls (eg, heparin, no prophylaxis), VOD/SOS incidence in controls was 16%. The risk ratio for developing VOD/SOS with defibrotide prophylaxis versus controls was 0.30 (95% confidence interval [CI] 0.12, 0.71; p=0·0002). No new safety concerns were reported in these studies.

The efficacy and safety of defibrotide in treatment of VOD have been extensively evaluated through the clinical development program over the last 20 years including approximately 2000 patients with VOD in multiple clinical trials and expanded access/compassionate use programs. In addition, defibrotide uses in clinical practice with > 15,000 patients treated with defibrotide post approval globally (Module 5.3.6/2020 PBRER) provides further evidence of the favorable safety profile of defibrotide in the currently-approved indication. Hepatic VOD remains a serious and life-threatening condition for thousands of patients in the world that if left untreated or sub-optimally treated can rapidly progress to multiple organ dysfunction and death (Coppell 2010). There is still a substantial unmet medical need to better manage patients with this condition. Defibrotide in the approved indication is well established in treatment of severe hepatic VOD. Efficacy of defibrotide was further supported with results from the pooled analysis of available evidence on defibrotide efficacy studies in the treatment of patients with VOD, including 17 studies representing 2598 patients. From this meta-analysis, survival rates at Day +100 were estimated at 54% pooled across all doses of defibrotide, and 56% in the approved dose of 25 mg/kg/day, which included n=2073 from 10 of the 17 studies (EMEA/H/C/002393/II/0043, June 2019). This represents comprehensive evidence on the efficacy and safety of defibrotide in the treatment of VOD, a potentially fatal condition post-HSCT, with a mortality >80% if left untreated (Coppell 2010). Estimated survival at Day +100 post-HSCT of 59.6% in participants who developed VOD and were treated with defibrotide rescue treatment (Table 14.2.6.1.7a) in Study 15-007 is consistent with results from previous studies and the above-described pooled analysis. No new safety concern has been raised from reported studies to date. The recently completed phase 2 study evaluating the efficacy of defibrotide in the prevention of acute GvHD included 152 adults and pediatric patients has shown similar safety data between defibrotide prophylaxis versus standard of care (Module 5.3.5.1/JZP963-201 CSR). Safety data in this additional randomized study on defibrotide were consistent with the safety profile of defibrotide. Furthermore, it is worth noting that defibrotide has been available since the 1980's and has been used in thousands of patients globally. No new safety signals have been raised from multiple use both in previous indications and currently.

In summary, Study 15-007 provided additional safety data on defibrotide in a randomized setting, to fulfil the EMA-required Specific Obligation on safety. Overall mortality is similar by the randomized treatment arms, in both the prophylaxis and rescue phase and by age group in the study. The safety results from this study are consistent with the defibrotide safety profile in treatment of VOD and evidence from earlier prevention and treatment studies in both pediatrics and adults. Comparison of the efficacy of defibrotide in the treatment of VOD in Study 15-007 is not appropriate. The group of participants who were diagnosed with VOD by EPAC only and did not receive defibrotide rescue treatment either did not have clinical VOD or had only very mild VOD for whom defibrotide rescue was deemed unnecessary per PI assessment; therefore, not appropriate or valid to compare with clinically-established severe form of VOD diagnosed by the PI and who received defibrotide rescue. These subgroups defined by post-randomization occurrence of VOD are not randomized groups and hence not

comparable in the severity of VOD and prognostic characteristics. Caution should be exercised when comparing subgroups that were not prespecified nor anticipated from the study design.

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Assessment of the MAH's response

Differences in outcome between EPAC-adjudicated cases of VOD and investigator-assessed cases of VOD

The external blinded endpoint adjudication committee (EPAC) is considered a clear strength of study 15-007, given the open-label study design, the severity of underlying disease in the study population, the need of stringency in establishing the diagnosis of VOD and and the difficulties in assessing other clinical data on use of defibrotide. The EPAC was provided with clinical data to assess whether VOD occurred or not. It is fully agreed that establishing the diagnosis of VOD could be difficult. The limitations with the modified Seattle criteria are also well known. Nevertheless, for study 15-007, both

the EPAC and the principal investigators appear to have had access to similar clinical data and utilised the same criteria for diagnosis. There appears to be no actual clinical data of importance for the diagnostic process that were taken into account by investigators but not provided to the EPAC. Thus, the discordance between investigators and the EPAC may not only be accounted for by the investigator being close to the patient, but also by an underlying bias resulting from investigators being non-blinded to study treatment. Notably, the authorisation of defibrotide relied on clinical data from one open-label pivotal trial with a historical control group for which VOD was retrospectively assessed. Therefore, the MAH argumentation warrants some caution regarding any lack of robustness of retrospective, remote assessment of VOD.

The overall mortality among those who received defibrotide as rescue treatment was higher as compared to those who were diagnosed by the EPAC only (and were not treated with defibrotide); 11/61 or 18% of EPAC-only diagnosed subjects died as compared to 23/43 or 53.5% of those who were diagnosed by both EPAC and investigators (and were treated with defibrotide). A key question is if any clinical differences were reported at the time of diagnosis between those diagnosed by investigators and those diagnosed by the EPAC but not by investigators. No such comprehensive discussion has been provided; rather, the discussion provided pertains to differences in risk factors for VOD, which may not translate into differences in severity if VOD actually occurs, and a difference in the proportion of cases with elevated bilirubin:

For risk factors for VOD at baseline, some differences are noted between those with a VOD diagnosis by the EPAC and those diagnosed by investigators only. However, several well recognised risk factors have not been included among the presented data, such as (degree of) liver disease, pulmonary function and underlying disease (ie cause of HSCT). Unrelated donors appear more frequent among those diagnosed by the EPAC only, whereas myeloablative conditioning was more frequent among those who received defibrotide as rescue treatment (including busulfan and fludarabine conditioning). More than half of patients in both groups had a 'very high risk' of VOD, 27/43 or 62.8% among those diagnosed by investigators and 32/61 or 52.5% of those diagnosed by the EPAC. Nevertheless, the relevance of these data to support whether subjects actually had VOD or not is unclear.

The extensive argumentation on why EPAD-diagnosed subjects with VOD actually did not actually have VOD is noted; notably, this could question the entire study design given that the primary endpoint was EPAC-adjudicated VOD. It is argued that among EPAC-adjudicated cases of VOD, a differential diagnosis or causal factor was often more likely than actual VOD, examples including preparative regimen, chemotherapy, pre-existing liver disease, underlying malignancy, or temporary condition such as volume overload. However, these factors are well known risk factors and/or symptoms of VOD and thus, the argumentation is somewhat difficult to follow. The only clinical factor that is described to differ between subjects diagnosed as VOD by both investigators and the EPAC, and those diagnosed by the EPAC only, is elevation of bilirubin; notably, however, subjects diagnosed only by investigators were older (median age 17 years; Table 1 above) than EPAC-diagnosed subjects (median age 10 years); anicteric VOD is well known to be more frequent among paediatric patients. Further, according to the protocol, defibrotide was used for treatment of VOD regardless of severity with VOD diagnosis as per the modified Seattle criteria in either the DP or BSC arms. Thus, it appears that defibrotide was not only to be used in cases of severe VOD (labelled indication) but for any VOD that developed as per investigators assessment.

A comparison between survival in EPAC-diagnosed VOD and patients post-HSCT without VOD in a publication from 2003 is not considered of limited value, given that EPAC-diagnosed subjects appear to have fulfilled the modified Seattle criteria and that there are considerable differences in treatment regimens used for conditioning as well as regarding the populations eligible for HSCT between contemporary care as compared to older data.

Mortality

Non-relapse mortality was a secondary endpoint of study 15-007 and was defined as death that occurs after HSCT in participants who were noted as having malignant primary disease on the disease history eCRF and who did not have primary disease relapse post-HSCT. Only participants with malignant primary disease at baseline were included in the analysis. As discussed in previous rounds, some caution is warranted given that the primary endpoint was not met; however, a cause of concern was the numerical imbalance in non-relapse mortality between participants in the defibrotide arm and the best supportive care arm. Of the participants with malignant primary disease history, 22 of 147 participants (15.0%) in the DP arm and 11 of 139 participants (7.9%) in the BSC arm experienced NRM by Day +100 post-HSCT. Of the participants with malignant primary disease history, 25 of 147 participants (17.0%) in the DP arm and 16 of 139 participants (11.5%) in the BSC arm experienced NRM by Day +180 post-HSCT. The vast majority of subjects had malignant disease as reason for their HSCT, and study deaths related to relapse or progression of malignant disease may be considered more likely not related to any study treatment as compared to non-malignant disease.

Despite the differences in NRM, it is however reassuring that there was no difference in overall mortality between the initial randomised treatment groups during the 'rescue phase'. The discussion on prevalence of risk factors for poor prognosis among those who actually died is not clearly relevant; rather, a discussion on risk factors for poor outcome for the respective entire treatment groups could have been more valuable. Notably, the treatment groups were balanced with regards to underlying disease. The numerical difference in non-relapse mortality between patients initially randomised to defibrotide-prophylaxis as compared to those initially randomised to best supportive care is considered to further substantiate that the benefit-risk of defibrotide for prophylaxis of VOD is negative.

A recent meta-analysis/systematic review on defibrotide prophylaxis of VOD is referred (Corbacioglu 2020), funded by the MAH and provided as a conference poster. Among the defibrotide prophylaxis studies included, the only new randomised controlled study included was Kikuta 2018, in which 50 patients undergoing myeloablative conditioning before allogenic HSCT were randomised to open-label defibrotide (N=33) or SoC (N =17). VOD/SOS occurred by day +30 post-HSCT in 1 (3.1%) patient in the defibrotide prophylaxis group vs no (0%) patients in the control group. Serious adverse events were reported in 8 (24.2%) patients in the defibrotide group and 2 (11.8%) were reported in control.

During the MA assessment and re-examination procedure, the data on prophylaxis (primarily the randomised study 2004) were not considered to support a relevant efficacy based also on the study design (open-label, investigator-based diagnosis of VOD). For safety, it was pointed out that the death rate was higher in the prevention study when children who did not develop VOD and received defibrotide were compared with subjects in the control arm who did not develop VOD still remained unexplained. Overall in the prevention trial a higher death rate of 25 (17%) in the defibrotide arm compared with 18 (13%) in the control arm was noted. Although most deaths occurred more than 1 month after cessation of defibrotide, in 7 cases AEs related to the death occurred during treatment with defibrotide or within one week of stopping defibrotide.

In conclusion, the requested data have been provided. Patients diagnosed as VOD by the EPAC only, and not receiving 'rescue treatment' with defibrotide had a clearly more favourable outcome regarding mortality. The MAH argumentation that those diagnosed by the EPAC actually did not have VOD, or had very mild VOD, is not considered adequately supported by clinical data. Thus, no firm conclusions can be drawn, and it is not likely that additional analyses could be of value. Notably, however, the discordance between investigators and the EPAC may not only be accounted for by the investigator being close to the patient, as argued by the MAH, but also by an underlying bias resulting from investigators being non-blinded to study treatment.

The difference in mortality disfavouring defibrotide prophylaxis during the first 30 days post HSCT remains unexplained. In addition to the concerns on overall mortality in the previous randomised defibrotide prophylaxis study (study 2004), the higher proportion of non-relapse mortality among patients randomised to defibrotide-prophylaxis as compared to best supportive care in study 15-007, and the absence of effect on prevention of VOD in study 15-007, the benefit-risk of defibrotide for prophylaxis of VOD is clearly negative.

Conclusion

Issue resolved.

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

14.2. Other concerns

Clinical aspects

Efficacy

Question 2. In table 4 in the response document, there are 96 events of VOD as assessed by the EPAC and 43 events of VOD as assessed by investigators (38 + 3 + 2) by Day +100 post-HSCT. However, with a reference to listing 16.2.7.3, it is stated that there were 56 participants diagnosed with VOD by investigators by Day +100. The MAH should clarify why these 13 participants are not included in the description of concordance between EPAC and investigators as outlined in Response Table 4.

Summary of the MAH's response
In the previously generated concordance analysis by Day +100 post-HSCT (Table 14.2.2.1.1), there are 31 participants in the modified Intent-To-Treat (mITT) Analysis Set who were excluded from the analysis using the VOD-free survival censoring rules for the primary efficacy endpoint (Module 5.3.5.4/JZP15-007 CSR/Section 8.8.6/Section 10.1). In one of those censoring rules, VOD-free survival is censored at the start of defibrotide rescue treatment. Out of these 31 participants, 13 were diagnosed with VOD by the Principal Investigator (PI) and started defibrotide rescue treatment, and therefore, were censored by this rule. The other 18 participants were censored for other reasons (EPAC-diagnosed VOD before HSCT [n=3] and death without VOD by Day +100 [n=15]). For the updated concordance analysis by Day +100 post-HSCT, these 31 subjects are included.

Since the final analysis of Study 15-007 was done, the MAH implemented a revised standard for concordance analyses that aligns with current best practice for this type of time-to-event analysis in hematology/oncology clinical trials. Under the revised standard, concordance is defined for all participants in the mITT Analysis Set as agreement between the EPAC and the PI on the diagnosis of VOD (both yes or both no), and in the case that VOD is diagnosed, diagnosis dates within 3 days. The Agency is asked to refer to the revised concordance analyses provided in this response (Table 5 and Table 6) instead of the previous ones. The results from the revised concordance analysis have been used in the responses to the major objection, Question 1.

The overall concordance between EPAC and PI diagnosis of VOD at Day +30 post-HSCT was 73.7% (Table 5). There was agreement that 233/353 participants (66%) did not have VOD and that 27/353 (7.7%) did have VOD with diagnosis dates within 3 days. Another 10/353 participants (2.8%) were diagnosed with VOD by both EPAC and PI, but the diagnosis dates were more than 3 days apart. At

Day +100 post-HSCT, the concordance rate was 51.6% (Table 6): 152/353 (43.1%) participants did not have VOD by EPAC and PI and 30/353 (8.5%) did have VOD with diagnosis dates within 3 days.

To explain this decrease in the concordance rate between Day +30 and Day +100 post-HSCT, consider the change in EPAC assessment from Day +30 to Day +100. There were 85 participants who were assessed by the EPAC as not having VOD by Day +30 ('No') who were assessed as 'Not Evaluable' or 'Yes' by EPAC at Day +100. Of the n=353 participants in the mITT Analysis Set, 14/353 (4.0%) had VOD assessed by EPAC as not having VOD by Day +30 and then as having VOD ('Yes') by Day +100 and matched the PI assessment by Day +100. Therefore, 71/353 (20.1%) changed from 'No' by Day +30 to 'Not Evaluable' by Day +100. Those who were not evaluable by EPAC could not be concordant. Similarly, of the 353 participants in the mITT Analysis Set, 43/353 (12.2%) were diagnosed by both EPAC and PI at Day +100; 30/353 (8.5%) had diagnosis dates within 3 days and were concordant, but 13/353 (3.7%) diagnosed by both EPAC and PI at Day +100 had dates that were more than 3 days part, further reducing the overall concordance rate.

Table 5: Concordance between Investigator and EPAC Assessed VOD by Day +30 Post-HSCT (Study 15-007; mITT Analysis Set)

Characteristic	DP (N=179)	BSC (N=174)	Total (N=353)
Investigator VOD/EPAC Assessed VOD			
Yes/Yes	18 (10.1)	19 (10.9)	37 (10.5)
Yes/No	4 (2.2)	9 (5.2)	13 (3.7)
No/Yes	31 (17.3)	22 (12.6)	53 (15.0)
No/No	115 (64.2)	118 (67.8)	233 (66.0)
Yes/Not Evaluable	1 (0.6)	1 (0.6)	2 (0.6)
No/Not Evaluable	10 (5.6)	5 (2.9)	15 (4.2)
Investigator VOD/EPAC Assessed VOD = Yes/Yes			
n	18	19	37
Yes/Yes – VOD Diagnosis Dates Match	14 (77.8)	13 (68.4)	27 (73.0)
Yes/Yes – Diagnosis dates: INV before EPAC	2 (11.1)	2 (10.5)	4 (10.8)
Yes/Yes – Diagnosis dates: INV after EPAC	2 (11.1)	4 (21.1)	6 (16.2)
Overall Concordance			
Yes/Yes and Diagnosis dates match + No/No	129 (72.1)	131 (75.3)	260 (73.7)

Abbreviations: DP=Defibrotide Prophylaxis; BSC=Best Supportive Care; EPAC=Endpoint Adjudication Committee; HSCT-hematopoietic stem cell transplant; mITT=modified intent-to-treat; VOD=Veno-Occlusive Disease

Notes:
[1] Percentages for Investigator VOD/EPAC Assessed VOD agreement and Overall Concordance were calculated using the number of participants in each arm from the mITT Analysis Set as the denominator.
[2] Percentages for matching diagnosis dates were calculated using the total number of the Yes/Yes category in each arm as the denominator.
[3] There are 3 participants in the No/Yes (Investigator VOD/EPAC Assessed VOD) category with an EPAC-assessed VOD dated prior to date of HSCT.
[4] In the Yes/Yes category, diagnosis dates are considered matched, if the difference between the diagnosis dates by investigator and by EPAC was less than or equal to 3 days.
[5] In the Yes/Yes category, the Investigator before EPAC category includes all participants whose dates of VOD diagnosis by investigator were more than 3 days before the dates of EPAC assessed VOD.
[6] In the Yes/Yes category, the Investigator after EPAC category includes all participants whose dates of VOD diagnosis by investigator were more than 3 days after the dates of EPAC assessed VOD.

Source: Table 2.2.1

Table 6: Concordance between Investigator and EPAC Assessed VOD by Day +100 Post-HSCT (Study 15-007; mITT Analysis Set)

Characteristic	DP (N=179)	BSC (N=174)	Total (N=353)
Investigator VOD/EPAC Assessed VOD			
Yes/Yes	19 (10.6)	24 (13.8)	43 (12.2)
Yes/No	3 (1.7)	6 (3.4)	9 (2.5)
No/Yes	36 (20.1)	25 (14.4)	61 (17.3)[a]
No/No	71 (39.7)	81 (46.6)	152 (43.1)
Yes/Not Evaluable	3 (1.7)	1 (0.6)	4 (1.1)
No/Not Evaluable	47 (26.3)	37 (21.3)	84 (23.8)
Investigator VOD/EPAC Assessed VOD = Yes/Yes			
n	19	24	43
Yes/Yes – VOD Diagnosis Dates Match	15 (78.9)	15 (62.5)	30 (69.8)
Yes/Yes – Diagnosis dates: INV before EPAC	2 (10.5)	5 (20.8)	7 (16.3)
Yes/Yes – Diagnosis dates: INV after EPAC	2 (10.5)	4 (16.7)	6 (14.0)
Overall Concordance			
Yes/Yes and Diagnosis dates match + No/No	86 (48.0)	96 (55.2)	182 (51.6)

Abbreviations: DP=Defibrotide Prophylaxis; BSC=Best Supportive Care; EPAC=Endpoint Adjudication Committee; HSCT-hematopoietic stem cell transplant; mITT=modified intent-to-treat; VOD=Veno-Occlusive Disease

[a] One participant was diagnosed with VOD by the Investigator after Day +100 Post-HSCT (and by EPAC on Day +11); therefore, considered "No" for Investigator VOD by Day +100 Post-HSCT and included in this category.

Notes:
[1] Percentages for Investigator VOD/EPAC Assessed VOD agreement and Overall Concordance were calculated using the number of participants in each arm from the mITT Analysis Set as the denominator.
[2] Percentages for matching diagnosis dates were calculated using the total number of the Yes/Yes category in each arm as the denominator.
[3] There are 3 participants in the No/Yes (Investigator VOD/EPAC Assessed VOD) category with an EPAC-assessed VOD dated prior to date of HSCT.
[4] In the Yes/Yes category, diagnosis dates are considered matched, if the difference between the diagnosis dates by investigator and by EPAC was less than or equal to 3 days.
[5] In the Yes/Yes category, the Investigator before EPAC category includes all subjects whose dates of VOD diagnosis by investigator were more than 3 days before the dates of EPAC assessed VOD.
[6] In the Yes/Yes category, the Investigator after EPAC category includes all participants whose dates of VOD diagnosis by investigator were more than 3 days after the dates of EPAC assessed VOD.

Source: Table 2.2.2

Assessment of the MAH's response

The MAH has presented a revised analysis of the concordance between the EPAC and investigators diagnosis of VOD. The full rationale and extent of which the new analyses differ as compared to the previously presented ones are however unclear. It appears, however, that all subjects treated with defibrotide as 'rescue treatment' in line with being diagnosed with VOD by investigators are now included in the Table pertaining to the +100 Day post-HSCT. A further comment is that with the new analyses, there appears to be more subjects who were not evaluable by the EPAC at Day + 30 post-HSCT (N = 17) as compared to what was previously presented (N =13) which could have some relevance for the primary efficacy outcome assessment; however, the rationale for the reclassification/new analyses is unclear. Given the low absolute number, this issue is not pursued.

Conclusion

Issue not further pursued.

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

Safety

Question 3. Data on VOD-resolution in subjects diagnosed with VOD during study 15-007 should be provided, divided by those who received defibrotide and those diagnosed with VOD who did not receive defibrotide, for the entire study population and divided by age groups (paediatric subjects vs adults).

Summary of the MAH's response

In Study 15-007, an Endpoint Adjudication Committee (EPAC) was set up to provide independent, blinded, medical review and adjudication of VOD diagnosis for the analyses of the primary and key secondary endpoints in the study. EPAC-assessed VOD diagnosis was based on the Modified Seattle

Criteria (MSC), per study protocol, and was performed from electronic review of participants' data, remotely and retrospectively. The Principal Investigators (PIs) assessed individual participants for presence of VOD in real time based on MSC, per study protocol, and as part of the participants' clinical care and management. Upon the diagnosis of VOD and when applicable, defibrotide rescue treatment was administered as per PI's clinical judgement. Assessment of VOD resolution was also performed in real time by the PI and reported in the study electronic case report form (eCRF). Per EPAC charter, no data for assessment of VOD resolution was provided to EPAC.

Per the study protocol, all participants diagnosed with VOD by the PI received defibrotide rescue treatment, except for 1 participant in the best supportive care (BSC) arm (Participant ID 8108-1002), who was diagnosed with VOD by the PI but did not receive defibrotide rescue treatment. This participant was withdrawn from Study 15-007 on the date of VOD diagnosis. Since assessment of VOD resolution was based on PI assessment only, data on VOD resolution (Yes/No) are available only for all participants who were diagnosed with VOD by the PI (Module 5.3.5.4/JZP15-007 CSR/Section 5.1.2.6).

Per the agency's request, the MAH performed an additional analysis on VOD resolution in participants who were diagnosed with VOD by EPAC and received defibrotide rescue treatment (cases diagnosed by EPAC and PI with VOD, n=43) versus those who did not receive defibrotide rescue treatment (participants who were diagnosed with VOD by EPAC only, n=61). Further, it is important to point out that an additional 13 participants were diagnosed with VOD by the PI, but not by EPAC, who received defibrotide treatment. Therefore, a total of 57 participants were diagnosed with VOD by PI, all of whom but one (Participant ID 8102-1008), received defibrotide rescue treatment (Figure 1). These 2 groups (VOD treated with defibrotide and not treated) were defined from the substantive discrepancy between the PI- and EPAC-assessment of VOD (see Q2) and represent groups that are invalid for comparison, as described in responses to Q1a and Q1c. An analysis comparing the 2 groups described above is invalid for the following reasons:

• Participants with VOD diagnoses by EPAC and PI represent only a proportion (43/56 [76.8%]) of all VOD participants diagnosed by PI who received defibrotide rescue treatment and subsequently had assessment of VOD resolution (n=56), and hence the analysis is incomplete and invalid for interpretation.

• The study was not designed to evaluate defibrotide in treatment of VOD. If the PI and EPAC diagnoses, including diagnosis dates, were fully concordant, the group of participants with VOD who were not treated with defibrotide rescue treatment would not have resulted. Exploration into the diagnosis discrepancy is described in the response to Q1a, which indicate that EPAC-only diagnosed VOD not treated with defibrotide rescue are not true clinical VODs.

• VOD resolution data are not available for the participants diagnosed with VOD by EPAC only, and not deemed by the PI as needing rescue treatment; therefore, the requested comparison is not possible. These participants were not diagnosed with VOD by the PI, and it is highly unlikely that these participants diagnosed with VOD only by EPAC had experienced true clinical VOD (please refer to response to Q1a and discussion in Q1c).

Both analyses (based on EPAC- or PI-diagnosis of VOD) are presented for the overall intent-to-treat (ITT) population and by age groups (pediatric participants [≤ 16 years old] and adult participants [> 16 years]) as requested.

For this analysis, the MAH has reviewed the study data in more detail, looking at all relevant data collected, as well as the individual participant safety narratives. The MAH would like to clarify the following: Some data on VOD resolution were missing from the data field on the electronic case report form (eCRF) that was utilized for the final report analysis. However, upon further investigation, VOD resolution was captured within a different eCRF page. To add more clarity on VOD resolution, all

available and relevant data on VOD resolution as reported by the PI were captured to provide a complete picture for the participants with missing data (Listing 3.4). In Table 7 and Table 8 below, the analyses in the left column were done based on VOD resolution captured within a specific data field on the VOD assessment eCRF, hence include a number of participants with VOD resolution status missing. The tables also include an additional column to the right, presenting VOD resolution that includes additional information on VOD resolution from the participant safety narratives that was not properly captured in the VOD assessment eCRF. Listing 3.4 is provided for the participants who had VOD resolution changed based on available information from the narratives for clarity and reference.

Post hoc analysis of VOD resolution of participants diagnosed with VOD based on EPAC assessment by those who received or did not receive defibrotide rescue treatment: A total of 43 participants were diagnosed with VOD by both EPAC and PI and received defibrotide rescue treatment: 21 pediatric participants and 22 adult participants. (Table 7). Overall, among these 43 participants VOD resolution was 28.0%. A higher VOD resolution was seen in pediatric participants (42.8%) versus adults (13.6%). Based on the additional information available (Table 7, right column), a higher VOD resolution is observed in the overall population at 44.2%; pediatrics 47.6% and adults 40.9% compared with the previous analysis with several incomplete fields for VOD resolution status. An additional 61 participants (34 pediatric and 27 adult) were diagnosed with VOD by EPAC did not receive defibrotide rescue treatment nor had assessment for VOD resolution, therefore 100% of these participants are presented as VOD resolution unknown. Additional substantial differences in VOD risk factors between this group (VOD diagnosed by EPAC only who did not receive defibrotide rescue treatment) and VOD diagnosed by EPAC and PI (who then received defibrotide rescue) were presented in Q1a/Table 2. As such and per the discussion in Q1a, it is likely that this group did not experience clinical VOD, hence is not an appropriate comparator group for those who did. Please note that one of the 61 participants was diagnosed with VOD by PI but was withdrawn from the study on the date of VOD diagnosis (Participant ID 8108-1002), hence did not receive defibrotide rescue treatment and therefore, was included in the participants not treated with defibrotide as rescue treatment in Table 7.

Table 7: VOD Resolution as per PI assessment in Participants with EPAC-Assessed VOD through Day +100 post-HSCT by Defibrotide Rescue Treatment (Yes/No) and Age Group (ITT Analysis Set)

Age Group Subgroup – Receiving Defibrotide as Rescue Treatment or Not Variable, Statistic	Participants with EPAC-Assessed VOD through Day +100 post-HSCT	
	With VOD Resolution Status missing	With information on VOD Resolution on all participants[a]
Overall, n (%)		
Participants Treated with Defibrotide as Rescue Treatment	**43**	**43**
VOD Resolved	12 (28.0)	19 (44.2)
VOD Not Resolved	20 (46.5)	24 (55.8)
VOD Resolution Status Missing[b]	11 (25.5)	0
Participants Not Treated with Defibrotide as Rescue Treatment	**61**	-
VOD Resolved	0	-
VOD Not Resolved	0	-
VOD Resolution Status Missing[b]	61 (100.0)	-

Age Group Subgroup – Receiving Defibrotide as Rescue Treatment or Not Variable, Statistic	Participants with EPAC-Assessed VOD through Day +100 post-HSCT	
	With VOD Resolution Status missing	With information on VOD Resolution on all participants[a]
Pediatric Participants (<=16 years), n (%)		
Participants Treated with Defibrotide as Rescue Treatment	**21**	**21**
VOD Resolved	9 (42.8)	10 (47.6)
VOD Not Resolved	7 (33.3)	11 (52.4)
VOD Resolution Status Missing[b]	5 (23.8)	-
Participants Not Treated with Defibrotide as Rescue Treatment	**34**	-
VOD Resolved	0	-
VOD Not Resolved	0	-
VOD Resolution Status Missing[b]	34 (100.0)	-
Adult Participants (>16 years), n (%)		
Participants Treated with Defibrotide as Rescue Treatment	**22**	**22**
VOD Resolved	3 (13.6)	9 (40.9)
VOD Not Resolved	13 (59.0)	13 (59.1)
VOD Resolution Status Missing[b]	6 (27.2)	0
Participants Not Treated with Defibrotide as Rescue Treatment	27	-
VOD Resolved	0	-
VOD Not Resolved	0	-
VOD Resolution Status Missing[b]	27 (100.0)	-

Abbreviations: eCRF=electronic case report form; EPAC=Endpoint Adjudication Committee; HSCT=hematopoietic stem cell transplant; VOD=Veno-Occlusive Disease

[a] Includes information on VOD resolution that was not captured on the eCRF VOD assessment from but sourced from patient narratives

[b] The category of VOD Resolution Status Missing includes all participants whose VOD resolution information was not collected. Participants with EPAC-assessed VOD but without investigator-diagnosed VOD have unknown VOD resolution status, because VOD resolution information was only collected for subjects with investigator-diagnosed VOD.

Notes: n = the number of subjects with EPAC-assessed VOD by Defibrotide rescue treatment and age group. Percentages were calculated with n as the denominator.

Source Table 14.2.9.5.3, Listing 3.4

Post hoc analysis of VOD resolution in participants diagnosed with VOD based on PI assessment and who received defibrotide treatment: Of the 56 participants diagnosed with VOD by the PI, an equal proportion had VOD resolved (39.3%) and not resolved (39.3%); 21.4% had missing VOD resolution status (Table 8). A higher percentage of pediatric participants (53.3%) had VOD resolution compared with adult participants (23.1%). Evaluation of the analysis that includes the additional information on VOD resolution from missing status cases (Table 8, right column), showed among the 56 participants with VOD diagnoses by PI, 50.0% had VOD resolution and 50.0% did not. The higher resolution of VOD in pediatric participants (56.7%) was maintained versus adult participants (42.3%).

Table 8: VOD Resolution in Participants with PI-Diagnosed VOD who received Defibrotide Rescue Treatment and Age Group (ITT Analysis Set)

Age Group Subgroup – Receiving Defibrotide as Rescue Treatment or Not Variable, Statistic	Participants with PI-Assessed VOD through Day +100 post-HSCT	
	With VOD Resolution Status missing	With information on VOD Resolution on all participants[a]
Overall, n (%)		
Participants Treated with Defibrotide as Rescue Treatment	**56**	**56**
VOD Resolved	22 (39.3)	28 (50.0)
VOD Not Resolved	22 (39.3)	28 (50.0)
VOD Resolution Status Missing[b]	12 (21.4)	0
Pediatric Participants (<=16 years), n (%)		
Participants Treated with Defibrotide as Rescue Treatment	**30**	**30**
VOD Resolved	16 (53.3)	17 (56.7)
VOD Not Resolved	8 (26.7)	13 (43.3)
VOD Resolution Status Missing[b]	6 (20.0)	-
Adult Participants (>16 years), n (%)		
Participants Treated with Defibrotide as Rescue Treatment	**26**	**26**
VOD Resolved	6 (23.1)	11 (42.3)
VOD Not Resolved	14 (53.8)	15 (57.7)
VOD Resolution Status Missing[b]	6 (23.1)	-

Abbreviations: eCRF=electronic case report form; EPAC=Endpoint Adjudication Committee; HSCT=hematopoietic stem cell transplant; VOD=Veno-Occlusive Disease

[a] Includes information on VOD resolution that was not captured on the eCRF VOD assessment form, but sourced from participant safety narratives

[b] The category of VOD Resolution Status Missing includes all participants whose VOD resolution information was not collected. Participants with EPAC-assessed VOD but without investigator-diagnosed VOD have unknown VOD resolution status, because VOD resolution information was only collected for subjects with investigator-diagnosed VOD.

Note: One adult participant (81018-1002) with investigator-diagnosed VOD withdrew from the study on the date of VOD diagnosis, and this participant was included in the Not Treated with Defibrotide as Rescue Treatment subgroup.

Source Table 14.2.9.6.2; Listing 3.4

In summary, the additional investigation of VOD resolution, utilizing all relevant clinical and safety data collected and specifically, individual participant safety narratives, provides a more complete picture of VOD resolution. Regardless of VOD diagnosis by EPAC or PI, VOD resolution was higher for pediatric participants compared to adult participants following treatment with defibrotide.

VOD resolution for participants who were diagnosed with VOD by EPAC only (and not the PI) is not available. Because this group was not diagnosed with VOD by PI, these participants did not receive defibrotide rescue treatment, nor did they have assessment of VOD resolution. The MAH would like to highlight that these participants either did not experience clinical VOD or at most may have had mild VOD cases that required no defibrotide rescue treatment, as assessed by the PI. Whereas, as described in response to Q1a, the participants with VOD diagnosed by the PI and treated with defibrotide were more definitive clinical cases of VOD with more advanced presentations (ie, the indication population per the Summary of Product Characteristics [SmPC]). These 2 groups are not valid comparators.

Despite the discrepancy in EPAC and PI VOD diagnoses, results on VOD resolution in participants who received defibrotide rescue treatment are consistent with known efficacy of defibrotide (Defitelio SmPC 2021).

Assessment of the MAH's response

The MAH states that VOD resolution data are not available for the participants diagnosed with VOD by EPAC only, and thus, no comparison can be made. As discussed in the previous round, based on the

protocol, given the extensive follow-up of participants up to Day +180 post-HSCT according to the protocol, with weekly assessment of VOD and VOD-associated MOD up to day +60 post-HSCT, and at Day +100 post-HSCT and day +180 post-HSCT, it should likely be possible to assess whether patients diagnosed with VOD by the EPAC had VOD resolution during the course of the study.

These data were requested given that this SOB also pertains to comparative safety data for defibrotide. If there is no difference on resolution of VOD in participants with VOD depending on treatment with defibrotide or not, then this is primarily a matter of lack of efficacy, which may not necessarily be a safety problem. However, if there was less resolution of VOD among those who received defibrotide for rescue treatment as compared to those who did not receive defibrotide for rescue treatment, then this is a potential safety problem.

The Rapporteur however agrees that no such evaluation was prespecified in the protocol; it is assumed that the MAH has carefully reviewed these data without considering any safety issue to be found. This issue is not pursued.

Conclusion

Issue not further pursued.

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

Question 4. The immunogenicity data should be provided within this procedure

Summary of the MAH's response

The Study 15-007 immunogenicity report has been provided, located in Module 5.3.5.4/JZP15-007 CSR/Immunogenicity Report):

The MAH efforts to develop an assay to detect the formation of anti-defibrotide Anti-Drug Antibodies (ADA) in humans have been unsuccessful as per report 0058-17, titled "Generation and Purification of Polyclonal Antibodies against Defibrotide in Rabbits" (Appendix 1). Since a validated ADA assay could not be developed, the commercially available anti-nuclear antibody (ANA) test, which can detect anti-DNA antibodies, has been employed in lieu of the ADA assay and neutralizing antibodies assays to evaluate and characterize defibrotide immunogenicity potential, and its results are presented in the current report.

In total 302 participants (out of 355 in the safety set) were included into the Immunogenicity Analysis Set, 157 in the defibrotide prophylaxis group and 145 in the best supportive care group; the weight restrictions limited the number of participants contributing to Immunogenicity Analysis Set.

Of the 136 participants who received defibrotide as prophylaxis and did not develop investigator diagnosed VOD, none had positive baseline ANA results. Most participants in this group had negative post-baseline results through Day +180 post-HSCT, and only 1 participant had a single positive post-baseline ANA result at Day +180 post-HSCT, measured as a low ANA titer (1:80). Of the 21 participants who received defibrotide as prophylaxis but developed investigator diagnosed VOD and then also received defibrotide as a rescue treatment, none had positive baseline or post-baseline ANA results. Of the 118 participants who received BSC as prophylaxis and did not develop investigator diagnosed VOD, 1 participant had a positive baseline ANA result measured as a high ANA titer (1:2560). A limited number of participants in this group had their post-baseline samples analyzed, but none had positive post-baseline results. Of the 27 participants who received BSC as prophylaxis but developed investigator diagnosed VOD and then received defibrotide as a rescue treatment, none had

positive baseline or post-baseline ANA results. These results indicate that defibrotide has a low immunogenicity risk in the studied population. There were no trends in ANA positive results or titer over the course of the study. There is no potential for predictive relationship between ANA status and clinical or safety measures of defibrotide.

Assessment of the MAH's response

There is no assay to detect anti-defibrotide ADAs as it was not possible to generate a positive control. Instead, a commercially available anti-nuclear antibody (ANA) test was employed, which is expected to be less specific to anti-defibrotide antibodies. As no positive control anti-defibrotide antibody is available, it is not possible to assess the adequacy of the ANA method either. There is no discussion on the immunogenicity findings in relation to the reports of hypersensitivity, and there is no further testing provided for those individuals who presented with ANA positivity.

Conclusions

Issue not further pursued. No conclusions on immunogenicity can be drawn due to the lack of a test to detect anti-defibrotide ADAs.

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

Question 5. An analysis of subjects in study 15-007 who had pre-existing liver disease based on a defined medical condition of hepatic disorder at baseline should be provided. The safety profile should be discussed not only in relation to best supportive care but also in relation to the overall safety population.

Summary of the MAH's response

Safety analyses using the requested definition of pre-existing liver disease were performed for the subset of participants with hepatic disorders at baseline. A participant was determined to have pre-existing liver disease only if they had a medical condition at baseline within the broad Hepatic disorders standardized MedDRA query (SMQ). This included analyses for the overall Safety Analysis Set for Study 15-007 in the defibrotide prophylaxis (DP) arm (N=181), as well as the pediatric (≤ 16 years old; n=99) and adult (> 16 years, n=82) subgroups in the DP arm. Of note, baseline was defined in the Study 15-007 protocol as the day before conditioning begins for participants in the DP arm, and on the day that conditioning begins for participants in the best supportive care (BSC) arm.

The safety profile in participants (all ages) with pre-existing liver disease in the DP arm (n=59) was compared with those participants having pre-existing liver disease in the BSC arm (n=62), as well as those participants who did not have pre-existing liver disease in the DP arm (n=122). This latter analysis was performed to determine if there was any impact on the overall safety population (in participants who received defibrotide for prophylaxis). The most common types of pre-existing liver disease seen in the DP arm included alanine aminotransferase (ALT) increased/aspartate aminotransferase (AST) increased, hepatic enzyme increased, hepatic steatosis, hepatomegaly, and transaminases increased (3 participants each; Table 14.1.6a). The most common types of pre-existing liver disease in the BSC arm included hepatic function abnormal (5 participants), hepatic steatosis and transaminases increased (4 participants each), and hepatic enzyme increased, hepatomegaly, aspartate aminotransferase increased, and hepatitis B (3 participants each).

The first portion of this response will describe the comparison of safety of defibrotide in participants with pre-existing liver disease across the 2 treatment arms (DP and BSC arms). The review will cover safety in the prophylaxis and rescue phases separately. The latter half of the response will evaluate the impact participants in the DP arm with pre-existing liver disease had on the overall safety population

by comparing this group to participants in the DP arm without pre-existing liver disease. The review will cover safety in the prophylaxis and rescue phases separately.

Comparison of Participants with Pre-existing Liver Disease by Treatment Arm – Prophylaxis Phase

During the prophylaxis phase of Study 15-007, a similar number of participants were identified as having pre-existing liver disease in the DP arm (n=59) and BSC arm (n=62). More pediatric participants (n=39) than adult participants (n=20) with pre-existing liver disease were randomized to the DP arm, and a similar number of pediatric and adult participants with pre-existing liver disease were randomized to the BSC arm (pediatric n=29; adult n=33).

During the prophylaxis phase of Study 15-007, the overall safety results in participants with pre-existing liver disease were similar in the DP and the BSC arms. The frequencies of the most common treatment-emergent adverse events (TEAEs; defined by occurrence in ≥ 15% of participants in either treatment arm) were generally similar in participants with pre-existing liver disease in the DP and BSC arms.

In a tabulated summary (see Table 9 of response document), the Preferred Terms (PTs) that were reported with a ≥ 10% higher frequency in the DP arm compared with the BSC arm included abdominal pain, blood bilirubin increased, headache, hyperglycaemia, hypertension, hypomagnesaemia, neutropenia, thrombocytopenia, and vomiting. The PTs that were reported by a ≥ 10% higher frequency in the BSC arm compared with the DP arm included hyperphosphataemia, insomnia, and neutrophil count decreased.

A notable pattern in this analysis was the higher incidences of TEAEs by PTs associated with myelosuppression (neutropenia, thrombocytopenia, and anemia) for the participants with pre-existing liver disease in the DP arm compared with the BSC arm. This difference is partially offset by the higher incidences observed in the BSC arm for the equivalent PTs falling under the System Organ Class (SOC) of Investigations (neutrophil count decreased and platelet count decreased). A likely contributing factor to the higher rates of myelosuppression terms observed for these participants in the DP arm is the higher proportion of pediatric to adult participants in this subgroup and arm compared to the same subgroup in the BSC arm. There were approximately twice as many pediatric versus (vs) adult participants in the DP arm with pre-existing liver disease compared to a roughly equivalent number of pediatric to adult participants in the BSC arm with pre-existing liver disease. The safety analysis performed for the overall Safety Analysis Set showed the incidence of myelosuppressive terms were significantly higher in pediatric compared with adult participants in both treatment arms (Module 5.3.5.4/JZP15-007 CSR/Table 14.3.1.4). For example, in the overall safety population, a higher percentage of pediatric participants compared to adult participants reported febrile neutropenia (19.9% vs 8.8%, respectively in the DP arm; 19.5% vs 15.5%, respectively in the BSC arm), anaemia (16.0% vs 10.5%, respectively in the DP arm; 18.4% vs 11.5%, respectively in the BSC arm), and neutropenia (10.5% vs 6.6%, respectively in the DP arm; 9.8% vs 5.7%, respectively in the BSC arm). Of note, all TEAEs associated with myelosuppression were considered unrelated to study drug during both the prophylaxis and rescue phases (Module 5.3.5.4/JZP15-007 CSR/Table 14.3.1.6). Pediatric patients undergoing hematopoietic stem cell transplant (HSCT) are likely to experience higher rates of myelosuppression due to differences in their underlying malignancy and a greater likelihood of treatment with myeloablative chemotherapy. Although many factors are considered in the selection of conditioning regimens, older age and poor performance status generally favors use of reduced intensity conditioning by physicians (Lee, 2008).

During the prophylaxis phase, serious treatment-emergent adverse events (TEAEs) were reported in a higher percentage of participants with pre-existing liver disease in the DP arm (44.1%) compared with

the BSC arm (32.3%; Table 14.3.7.5.2a). There was no specific pattern to the PTs that accounted for this moderate difference, as the majority of PTs were reported in only 1 participant. The only serious TEAEs reported in ≥ 2 participants with pre-existing liver disease in the DP arm were gastrointestinal haemorrhage (5.1%), hypotension (3.4%), pyrexia (3.4%), respiratory failure (3.4%) and sepsis (3.4%); and the only serious TEAEs reported in ≥ 2 participants with pre-existing liver disease in the BSC arm were acute graft-versus-host disease (GvHD) in intestine (3.2%), febrile neutropenia (3.2%), respiratory distress (3.2%), and stomatitis (3.2%). The percentage of participants with pre-existing liver disease who experienced at least 1 TEAE leading to death during the prophylaxis phase was similar in the DP and BSC arms (3.4% vs 3.2%, respectively; Table 14.3.7.5.5a).

During the prophylaxis phase, treatment-related TEAEs were reported in 22.0% of participants with pre-existing liver disease in the DP arm (Table 14.3.7.5.3a). The only treatment-related TEAEs reported in ≥ 2 participants were associated with bleeding and included the PTs of gastrointestinal hemorrhage (5.1%) and haematochezia (3.4%). Bleeding events are consistent with the known safety profile of defibrotide. As expected in this open-label study where the comparator arm consists of best supportive care, assessments of treatment relatedness were made only in the DP arm during the prophylaxis phase. During the prophylaxis phase, the overall incidence of bleeding events in participants with pre-existing liver disease was similar in the DP arm (47.5%) and BSC arm (43.5%; Table 14.3.7.5.6a). The overall incidence of thromboembolic events in participants with pre-existing liver disease was low and similar in the DP (6.8%) and BSC (4.8%) arms (Table 14.3.7.5.7a).

During the prophylaxis phase, within the DP arm, some PTs were reported with a ≥ 10% difference between the pediatric and adult participants having pre-existing liver disease. TEAEs occurring more frequently for the pediatric participants included engraftment syndrome, febrile neutropenia, hypomagnesaemia, neutropenia, pain, pyrexia, and thrombocytopenia (Table 14.3.7.5.1a). TEAEs occurring more frequently for the adult participants include diarrhoea, epistaxis, headache, hyperglycaemia, hypoalbuminaemia, nausea, and rash. For the events that showed a higher incidence in pediatric participants compared with adult participants in the DP arm, a consistent and similar difference in incidence was also generally seen between the pediatric and adult participants with pre-existing liver disease within the BSC arm. The pediatric participants with pre-existing liver disease in the DP arm had a lower incidence compared to the respective adult participants for serious TEAEs (41.0% vs 50.0%), treatment-related TEAEs (20.5% vs 25.0%), bleeding events (43.6% vs 55.0%), and thromboembolic events (2.6% vs 15.0%) (Table 14.3.7.5.2a, Table 14.3.7.5.3a, Table 14.3.7.5.6a, and Table 14.3.7.5.7a, respectively).

Comparison of Participants with Pre-existing Liver Disease by Treatment Arm – Rescue Phase

In the rescue phase of the study, a similar number of participants were identified as having pre-existing liver disease in the DP arm (n=12) and BSC arm (n=10). In addition, a similar number of pediatric and adult participants with pre-existing liver disease were included in the rescue phase by randomized treatment arm: DP arm (pediatric n=5; adult n=7) and BSC arm (pediatric n=5; adult n=5).

For participants with pre-existing liver disease during the rescue phase, the most commonly reported TEAE by PTs for those participants from the DP arm were VOD, diarrhoea, blood bilirubin increased, pleural effusion and pyrexia; and from the BSC arm, VOD, diarrheoa, acute kidney injury, hypertension, and hypotension (see Table 10 in response document). The most common events in either arm were associated with VOD that developed as a complication of HSCT. While the small subpopulations of participants with pre-existing liver disease in the rescue phase limits the safety analysis, no new safety signals associated with defibrotide were evident.

Further dividing the small numbers of participants with pre-existing liver disease in the rescue phase by age subgroups limits interpretation of any comparison. Overall, while there were some differences in the safety results between pediatric and adult participants with pre-existing liver disease, they were generally consistent and similar between the DP and BSC arms.

Comparison of Participants with Pre-existing Liver Disease by Treatment Arm – Vital Signs and Laboratory Results

For participants with pre-existing liver disease (overall, adult, and pediatric), Table 14.3.7.1.1a provides a summary of vital signs by treatment arm for baseline and Day +30 post- HSCT, with changes from baseline to Day +30 post-HSCT. Similarly, Table 14.3.7.1.2a provides a summary of vital signs by treatment arm at the time of diagnosis of VOD and Day +30 post-VOD rescue treatment, with changes from VOD diagnosis to Day +30 post-VOD rescue treatment.

Table 14.3.7.2.1a, Table 14.3.7.3.1a, and Table 14.3.7.4.1a provide summaries of hematology, chemistry, and coagulation laboratory results, respectively, in participants with pre-existing liver disease by treatment arm at baseline and Day +30 post-HSCT, with changes from baseline to Day +30 Post-HSCT. In this same subpopulation, Table 14.3.7.2.2a, Table 14.3.7.3.2a, and Table 14.3.7.4.2a provide summaries of hematology, chemistry, and coagulation laboratory results, respectively, by treatment arm at the time of diagnosis of VOD and Day +30 post-VOD rescue treatment, with changes from VOD diagnosis to Day +30 Post-VOD rescue treatment.

Overall, no clinically meaningful differences in the mean and median laboratory values and vital signs were observed between the DP and BSC treatment arms at the time points specified. Mean changes in laboratory parameters and vital signs from baseline to Day +30 post-HSCT were similar between the treatment arms for the overall population of participants with pre-existing liver disease, as well as both age subgroups. Although some substantial changes in laboratory values and vital signs from VOD diagnosis to Day +30 post-VOD rescue treatment were observed in the 2 treatment arms, the results should be interpreted with caution as the numbers of participants included in the rescue phase were small, and those with laboratory values and vital signs captured at both time points were even smaller.

Comparison of Participants in the DP arm with Pre-existing Liver Disease to those without Pre-existing Liver Disease – Prophylaxis Phase

During the prophylaxis phase of Study 15-007, a smaller number of participants in the DP arm were identified as having pre-existing liver disease at baseline (n=59) compared with the number of participants in the DP arm without pre-existing liver disease (n=122; Table 14.3.7.5.1b). Of this subpopulation with pre-existing liver disease in the DP arm, there were more pediatric (n=39) than adult (n=20) participants; however, for participants without pre-existing liver disease in the DP arm, a similar number of participants were included in these age subgroups (pediatric n=60; adult n=62).

The small number of participants with pre-existing liver disease and the imbalance between the subgroups with and without pre-existing liver disease should be considered when comparing the safety results. Participants with pre-existing liver disease represented only 32.6% (59/181) of the DP arm Safety Analysis Set.

During the prophylaxis phase, the overall safety results were similar for participants with and without pre-existing liver disease (Table 11). The frequencies of the most common TEAEs (defined by occurrence in ≥ 15% of overall participants) were generally similar in participants with and without pre-existing liver disease. The PTs that were reported with a ≥ 10% higher incidence for participants with pre-existing liver disease compared to those without pre-existing liver disease included abdominal pain, anaemia, blood bilirubin increased, engraftment syndrome, febrile neutropenia, hypoalbuminaemia, hypomagnesaemia, neutropenia, thrombocytopenia, vomiting, and weight

increased. Again, it is noted that participants with pre-existing liver disease showed a higher incidence of TEAEs associated with myelosuppression (anaemia, febrile neutropenia/neutropenia, and thrombocytopenia). This appears to be primarily driven by the higher proportion of pediatric participants in this pre-existing liver disease subgroup compared with participants without pre-existing liver disease. In general, as described above, pediatric participants had higher rates of myelosuppression-related TEAEs regardless of treatment arm.

Table 11: Treatment-Emergent Adverse Events ≥ 15% in Participants in the DP arm With or Without Pre-existing Liver Disease (Study 15-007 Prophylaxis Phase; Safety Analysis Set)

	Participants with Pre-Existing Liver Disease			Participants without Pre-Existing Liver Disease		
Preferred Term (MedDRA)	**Total n=59**	**Pediatric (≤16 yr) n=39**	**Adult (>16 yr) n=20**	**Total n=122**	**Pediatric (≤16 yr) n=60**	**Adult (>16 yr) n=62**
Number of Participants With at Least 1 TEAE, n (%)	**59 (100)**	**39 (100)**	**20 (100)**	**121 (99.2)**	**60 (100)**	**61 (98.4)**
Vomiting	38 (64.4)	26 (66.7)	12 (60.0)	65 (53.3)	38 (63.3)	27 (43.5)
Pyrexia	37 (62.7)	26 (66.7)	11 (55.0)	74 (60.7)	42 (70.0)	32 (51.6)
Stomatitis	37 (62.7)	24 (61.5)	13 (65.0)	68 (55.7)	38 (63.3)	30 (48.4)
Diarrhoea	32 (54.2)	19 (48.7)	13 (65.0)	73 (59.8)	32 (53.3)	41 (66.1)
Nausea	32 (54.2)	19 (48.7)	13 (65.0)	77 (63.1)	38 (63.3)	39 (62.9)
Hypomagnesaemia	29 (49.2)	21 (53.8)	8 (40.0)	42 (34.4)	26 (43.3)	16 (25.8)
Abdominal pain	24 (40.7)	15 (38.5)	9 (45.0)	33 (27.0)	19 (31.7)	14 (22.6)
Hypertension	24 (40.7)	17 (43.6)	7 (35.0)	44 (36.1)	17 (28.3)	27 (43.5)
Hypokalaemia	24 (40.7)	15 (38.5)	9 (45.0)	47 (38.5)	28 (46.7)	19 (30.6)
Febrile neutropenia	23 (39.0)	18 (46.2)	5 (25.0)	29 (23.8)	18 (30.0)	11 (17.7)
Anaemia	21 (35.6)	14 (35.9)	7 (35.0)	27 (22.1)	15 (25.0)	12 (19.4)
Decreased appetite	20 (33.9)	12 (30.8)	8 (40.0)	30 (24.6)	13 (21.7)	17 (27.4)
Headache	19 (32.2)	9 (23.1)	10 (50.0)	30 (24.6)	6 (10.0)	24 (38.7)
Neutropenia	16 (27.1)	13 (33.3)	3 (15.0)	15 (12.3)	6 (10.0)	9 (14.5)
Blood bilirubin increased	15 (25.4)	9 (23.1)	6 (30.0)	11 (9.0)	2 (3.3)	9 (14.5)
Thrombocytopenia	15 (25.4)	12 (30.8)	3 (15.0)	16 (13.1)	2 (3.3)	14 (22.6)
Epistaxis	13 (22.0)	7 (17.9)	6 (30.0)	26 (21.3)	14 (23.3)	12 (19.4)
Hypoalbuminaemia	13 (22.0)	6 (15.4)	7 (35.0)	14 (11.5)	11 (18.3)	3 (4.8)
Weight increased	12 (20.3)	7 (17.9)	5 (25.0)	10 (8.2)	4 (6.7)	6 (9.7)
Constipation	10 (16.9)	6 (15.4)	4 (20.0)	24 (19.7)	8 (13.3)	16 (25.8)
Hyperglycaemia	10 (16.9)	5 (12.8)	5 (25.0)	11 (9.0)	4 (6.7)	7 (11.3)
Platelet count decreased	10 (16.9)	7 (17.9)	3 (15.0)	23 (18.9)	16 (26.7)	7 (11.3)
Rash	10 (16.9)	5 (12.8)	5 (25.0)	19 (15.6)	10 (16.7)	9 (14.5)
Sinus tachycardia	10 (16.9)	7 (17.9)	3 (15.0)	24 (19.7)	21 (35.0)	3 (4.8)
Engraftment syndrome	9 (15.3)	8 (20.5)	1 (5.0)	5 (4.1)	2 (3.3)	3 (4.8)
Oedema peripheral	9 (15.3)	5 (12.8)	4 (20.0)	17 (13.9)	7 (11.7)	10 (16.1)
Pain	9 (15.3)	8 (20.5)	1 (5.0)	11 (9.0)	8 (13.3)	3 (4.8)
Acute graft versus host disease in skin	8 (13.6)	5 (12.8)	3 (15.0)	22 (18.0)	5 (8.3)	17 (27.4)
Hypotension	8 (13.6)	5 (12.8)	3 (15.0)	20 (16.4)	13 (21.7)	7 (11.3)

Abbreviations: DP=defibrotide prophylaxis; MedDRA=Medical Dictionary for Regulatory Activities; TEAE=treatment-emergent adverse event.
Source: Table 14.3.7.5.1a, Table 14.3.7.5.1b

During the prophylaxis phase, participants with and without pre-existing liver disease in the DP arm had similar incidences of serious TEAEs (44.1% vs 39.3%, respectively), fatal TEAEs (3.4% vs 6.6%, respectively), treatment-related AEs (22.0% vs 23.0%, respectively), bleeding events (47.5% vs 47.5%, respectively) and thromboembolic events (6.8% vs 4.9%, respectively).

Comparison of Participants in the DP arm with Pre-existing Liver Disease to those without Pre-existing Liver Disease – Rescue Phase

In the rescue phase, a similar number of participants identified as having pre-existing liver disease at baseline in the DP arm (n=12) compared with the number of participants without pre-existing liver disease in the DP arm (n=13; Table 12).

Within the rescue phase, for participants in the DP arm with pre-existing liver disease, the most commonly reported TEAE by PTs were VOD, diarrhoea, blood bilirubin increased, pleural effusion and pyrexia; and for participants in the DP arm without pre-existing liver disease, events included VOD, venoocclusive liver disease, and constipation. The most common events reported in the rescue phase for participants with or without pre-existing liver disease were associated with VOD that developed as a complication of HSCT. While the small numbers of participants with and without pre-existing liver disease included in the rescue phase limits the safety analysis, no new safety signals associated with defibrotide were evident.

Table 12: Treatment Emergent Adverse Events ≥ 20% in Participants in the DP arm With or Without Pre-existing Liver Disease (Study 15-007 Rescue Phase, Safety Analysis Set)

	Participants with Pre-Existing Liver Disease			Participants without Pre-Existing Liver Disease		
Preferred Term (MedDRA)	**Total n=12**	**Pediatric (≤16 yr) n=5**	**Adult (>16 yr) n=7**	**Total n=13**	**Pediatric (≤16 yr) n=10**	**Adult (>16 yr) n=3**
Number of Participants With at Least 1 TEAE, n (%)	**12 (100)**	**5 (100)**	**7 (100)**	**13 (100)**	**10 (100)**	**3 (100)**
Venoocclusive disease	6 (50.0)	2 (40.0)	4 (57.1)	8 (61.5)	5 (50.0)	3 (100)
Diarrhoea	6 (50.0)	2 (40.0)	4 (57.1)	1 (7.7)	1 (10.0)	0
Blood bilirubin increased	4 (33.3)	2 (40.0)	2 (28.6)	2 (15.4)	1 (10.0)	1 (33.3)
Pleural effusion	4 (33.3)	2 (40.0)	2 (28.6)	1 (7.7)	0	1 (33.3)
Pyrexia	4 (33.3)	0	4 (57.1)	2 (15.4)	2 (20.0)	0
Acute kidney injury	3 (25.0)	0	3 (42.9)	0	0	0
Alanine aminotransferase increased	3 (25.0)	2 (40.0)	1 (14.3)	0	0	0
Anaemia	3 (25.0)	1 (20.0)	2 (28.6)	2 (15.4)	1 (10.0)	1 (33.3)
Aspartate aminotransferase increased	3 (25.0)	2 (40.0)	1 (14.3)	0	0	0
Conjunctival haemorrhage	3 (25.0)	2 (40.0)	1 (14.3)	0	0	0
Constipation	3 (25.0)	1 (20.0)	2 (28.6)	4 (30.8)	4 (40.0)	0
Cough	3 (25.0)	1 (20.0)	2 (28.6)	0	0	0
Hypertension	3 (25.0)	1 (20.0)	2 (28.6)	3 (23.1)	3 (30.0)	0
Hypokalaemia	3 (25.0)	1 (20.0)	2 (28.6)	3 (23.1)	2 (20.0)	1 (33.3)
Platelet count decreased	3 (25.0)	2 (40.0)	1 (14.3)	2 (15.4)	2 (20.0)	0
Sinus tachycardia	3 (25.0)	0	3 (42.9)	1 (7.7)	0	1 (33.3)
Vomiting	3 (25.0)	2 (40.0)	1 (14.3)	2 (15.4)	2 (20.0)	0
Abdominal distension	2 (16.7)	1 (20.0)	1 (14.3)	3 (23.1)	2 (20.0)	1 (33.3)
Acute graft versus host disease in skin	1 (8.3)	1 (20.0)	0	3 (23.1)	2 (20.0)	1 (33.3)
Hypoalbuminaemia	1 (8.3)	1 (20.0)	0	3 (23.1)	2 (20.0)	1 (33.3)
Venoocclusive liver disease	1 (8.3)	0	1 (14.3)	4 (30.8)	4 (40.0)	0

Abbreviations: DP=defibrotide prophylaxis; MedDRA=Medical Dictionary for Regulatory Activities; TEAE=treatment-emergent adverse event.
Source: Table 14.3.7.5.1a, Table 14.3.7.5.1b

For participants in the DP arm with and without pre-existing liver disease, Table 14.3.7.1.1a and Table 14.3.7.1.1b, respectively, provide summaries of vital signs for baseline and Day +30 post-HSCT, with

changes from baseline to Day +30 post-HSCT. Similarly, Table 14.3.7.1.2a and Table 14.3.7.1.2b provide summaries of vital signs for participants in the DP arm with and without pre-existing liver, respectively, at the time of diagnosis of VOD and Day +30 post-VOD rescue treatment, with changes from VOD diagnosis to Day +30 post-VOD rescue treatment.

For participants in the DP arm with and without pre-existing liver disease, respective summaries at baseline, at Day +30 post-HSCT, and with changes from baseline to Day +30 Post-HSCT are provided for hematology (Table 14.3.7.2.1a and Table 14.3.7.2.1b), chemistry Table 14.3.7.3.1a and Table 14.3.7.3.1b, and coagulation (Table 14.3.7.4.1a and Table 14.3.7.4.1b) laboratory results. For participants in the DP arm with and without pre-existing liver disease, respective summaries at the time of diagnosis of VOD, at Day +30 post-VOD treatment, and with changes from VOD diagnosis to Day +30 Post-VOD rescue treatment are provided for hematology (Table 14.3.7.2.2a and Table 14.3.7.2.2b), chemistry (Table 14.3.7.3.2a and Table 14.3.7.3.2b), and coagulation laboratory results (Table 14.3.7.4.2a and Table 14.3.7.4.2b).

Although some substantial changes in laboratory values and vital signs from baseline to Day +30 post-HSCT and from VOD diagnosis to Day +30 post-VOD rescue treatment were observed between the subpopulations of participants with and without pre-existing liver disease in the DP arm, the results should be interpreted with caution as the numbers of participants with pre-existing liver disease were small, and smaller yet for those with laboratory values and vital signs captured at both time points analyzed.

Summary of Safety in Participants with Pre-existing Liver Disease

In this study, the safety of participants with pre-existing liver disease treated with defibrotide was generally consistent with the known safety profile of defibrotide and with clinical events commonly experienced in the population studied. Some differences in TEAE frequencies in participants in the DP arm with pre-existing liver disease compared to the respective subpopulation in the BSC arm, as well as participants in the DP arm without pre-existing liver disease may have resulted from the disproportional number of pediatric participants with pre-existing liver disease in the DP arm. In general, pediatric patients following HSCT may experience a different profile of clinical adverse events compared to adults, given differences in underlying malignancies and exposure to myeloablative conditioning regimens. No new safety signals were detected for participants with pre-existing liver disease and administered defibrotide.

References

Lee SJ, Joffe S, Artz AS, et al. Individual Physician Practice Variation in Hematopoietic Cell Transplantation. Journal of Clinical Oncology. 2008 May 1;26(13): 2162-70.

Assessment of the MAH's response

The requested analyses have been provided.

A similar number of participants had pre-existing liver disease, based on a defined medical condition of hepatic disorder at baseline, in the defibrotide prophylaxis arm (n=59) and BSC arm (n=62); however, among those, more paediatric subjects with pre-existing liver disease were randomised to the defibrotide arm. A higher rate of myelosuppression was reported among subjects with pre-existing liver disease in the defibrotide prophylaxis arm as compared to best supportive care. This is explained by the MAH to pertain to the higher proportion of paediatric subjects with pre-existing liver disease in that arm. Overall, serious TEAEs were reported in more subjects with pre-existing liver disease in the defibrotide arm as compared to best supportive care (44.1% vs 32.3%). Among serious TEAEs reported in 2 or more participants in the defibrotide arm, gastrointestinal haemorrhage was most

frequent (reported in 5.1% of subjects; haematochezia was however also reported among 3.4%); this is considered in line with an increased risk of bleeding with defibrotide as labelled.

The number of patients with pre-existing liver disease who were considered to have VOD by investigators and received rescue treatment with defibrotide was low (n = 22); there were no clear differences between those initially randomised to defibrotide prophylaxis and those randomised to best supportive care.

Extensive tabulations of PTs pertaining to laboratory test abnormalities, other hepatic findings and vital signs have been provided, divided by treatment arm and age group. There is no grouping of such PTs that could be considered related which hampers the assessment. However, overall, there are no apparent unexpected safety findings. Similar to the overall study population, laboratory values and/or vital signs were missing in many study participants.

For the comparison between patients with pre-existing liver disease in relation to those without such pre-existing disease, there are some differences regarding prophylaxis phase TEAEs that occurred more frequently among those with pre-existing liver disease, especially myelosuppression (anaemia, febrile neutropenia/neutropenia, and thrombocytopenia). The MAH again highlights that this could be due to a higher proportion of paediatric patients having pre-existing liver disease; however, there appears to be a higher proportion of anaemia and febrile neutropenia also among adults. Given the low absolute numbers of events, however, no conclusions can be made. It is somewhat reassuring that fatal TEAEs and bleeding events were balanced between participants with and without pre-existing liver disease in the defibrotide prophylaxis arm.

Overall, no firm conclusions on the safety of defibrotide in patients with pre-existing liver disease can be made, however, there are no new unexpected findings.

Conclusion

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

Question 6. The findings of hypertension, hypomagnesaemia and hypokalaemia in the defibrotide group among subjects with pre-existing renal insufficiency should be discussed in more detail, also in relation to the overall safety population.

Summary of the MAH's response

As in the previously-submitted analyses, a participant was determined to have pre-existing renal insufficiency if they had an abnormal renal function laboratory result at baseline, including a serum creatinine elevated above the normal reference range or glomerular filtration rate/creatinine clearance below the normal reference range.

<u>Comparison of Participants in the DP arm with Pre-existing Renal Insufficiency to those without Pre-existing Renal Insufficiency – Prophylaxis Phase</u>

During the prophylaxis phase of Study 15-007, only a small number of participants in the DP arm were identified as having pre-existing renal insufficiency at baseline (n=19) compared to participants without pre-existing renal insufficiency (n=162; Table 13). Of these subpopulations, there were more adult (n=15) than pediatric participants (n=4) with pre-existing renal insufficiency; and more pediatric (n=95) than adult participants (n=67) without pre-existing renal insufficiency in the DP arm. A meaningful comparison of safety for participants with pre-existing renal insufficiency to those without pre-existing renal insufficiency was limited due to the small population of such participants in Study 15-007. Participants with pre-existing renal insufficiency represented only 10.5% (19/181) of the DP arm safety population.

During the prophylaxis phase, the overall safety results were similar in participants with and without pre-existing renal insufficiency (Table 13). The frequencies of the most common treatment-emergent adverse events (TEAEs, defined by occurrence in ≥ 20% of participants) were generally comparable between participants with and without pre-existing renal insufficiency. The preferred terms (PTs) that were reported with a ≥ 10% higher frequency in participants with pre-existing renal insufficiency than without pre-existing renal insufficiency included decreased appetite, hypertension, and hypoalbuminaemia. The PTs that were reported by a ≥ 10% higher frequency in participants without pre-existing renal insufficiency than with pre-existing renal insufficiency included pyrexia, stomatitis, and vomiting.

Table 13: Treatment-Emergent Adverse Events ≥ 20% in Participants in the DP arm With or Without Pre-existing Renal Insufficiency (Study 15-007 Prophylaxis Phase; Safety Analysis Set)

	Participants with Pre-Existing Renal Insufficiency			Participants without Pre-Existing Renal Insufficiency		
Preferred Term (MedDRA)	**Total n=19**	**Pediatric (≤16 yr) n=4**	**Adult (>16 yr) n=15**	**Total n (%) n=162**	**Pediatric (≤16 yr) n=95**	**Adult (>16 yr) n=67**
Number of Participants With at Least 1 TEAE, n (%)	**18 (94.7)**	**4 (100)**	**14 (93.3)**	**162 (100)**	**95 (100)**	**67 (100)**
Diarrhoea	12 (63.2)	2 (50.0)	10 (66.7)	93 (57.4)	49 (51.6)	44 (65.7)
Hypertension	11 (57.9)	3 (75.0)	8 (53.3)	57 (35.2)	31 (32.6)	26 (38.8)
Nausea	10 (52.6)	2 (50.0)	8 (53.3)	99 (61.1)	55 (57.9)	44 (65.7)
Pyrexia	8 (42.1)	2 (50.0)	6 (40.0)	103 (63.6)	66 (69.5)	37 (55.2)
Decreased appetite	7 (36.8)	1 (25.0)	6 (40.0)	43 (26.5)	24 (25.3)	19 (28.4)
Hypomagnesaemia	7 (36.8)	2 (50.0)	5 (33.3)	64 (39.5)	45 (47.4)	19 (28.4)
Stomatitis	7 (36.8)	3 (75.0)	4 (26.7)	98 (60.5)	59 (62.1)	39 (58.2)
Vomiting	7 (36.8)	2 (50.0)	5 (33.3)	96 (59.3)	62 (65.3)	34 (50.7)
Abdominal pain	6 (31.6)	2 (50.0)	4 (26.7)	51 (31.5)	32 (33.7)	19 (28.4)
Febrile neutropenia	6 (31.6)	3 (75.0)	3 (20.0)	46 (28.4)	33 (34.7)	13 (19.4)
Hypokalaemia	6 (31.6)	3 (75.0)	3 (20.0)	65 (40.1)	40 (42.1)	25 (37.3)
Constipation	5 (26.3)	2 (50.0)	3 (20.0)	29 (17.9)	12 (12.6)	17 (25.4)
Epistaxis	5 (26.3)	1 (25.0)	4 (26.7)	34 (21.0)	20 (21.1)	14 (20.9)
Headache	5 (26.3)	0	5 (33.3)	44 (27.2)	15 (15.8)	29 (43.3)
Hypoalbuminaemia	5 (26.3)	2 (50.0)	3 (20.0)	22 (13.6)	15 (15.8)	7 (10.4)
Anaemia	4 (21.1)	1 (25.0)	3 (20.0)	44 (27.2)	28 (29.5)	16 (23.9)
Cytomegalovirus infection	4 (21.1)	1 (25.0)	3 (20.0)	20 (12.3)	10 (10.5)	10 (14.9)
Oedema peripheral	4 (21.1)	2 (50.0)	2 (13.3)	22 (13.6)	10 (10.5)	12 (17.9)

Abbreviations: DP=defibrotide prophylaxis; MedDRA=Medical Dictionary for Regulatory Activities; TEAE=treatment-emergent adverse event.
Source: Table 14.3.8.5.1, Table 14.3.8.5.1b

Serious TEAEs were reported in a higher percentage of participants in the DP arm without pre-existing renal insufficiency (42.0%; Table 14.3.8.5.2b) than with pre-existing renal insufficiency (31.6%; Table 14.3.8.5.2) in the prophylaxis phase. Of note, no specific PT was reported as a serious event in more than 2 participants with pre-existing renal insufficiency. Fatal TEAEs in the prophylaxis phase were reported in a similar percentage of participants in the DP arm with pre-existing renal insufficiency (5.3%; Table14.3.8.5.5) and without pre-existing renal insufficiency (5.6%; Table14.3.8.5.5b). Treatment-related TEAEs in the prophylaxis phase were reported in a higher percentage of participants

in the DP arm with pre-existing renal insufficiency (31.6%; Table 14.3.8.5.3) than without pre-existing renal insufficiency (21.6%; Table 14.3.8.5.3b). Consistent with the known safety profile of defibrotide, the majority of treatment-related TEAEs represented bleeding events in participants with and without pre-existing renal insufficiency.

During the prophylaxis phase, bleeding events overall were reported in a higher percentage of participants in the DP arm with pre-existing renal insufficiency (57.9% [Table 14.3.8.5.6]) than those participants without (46.3% [Table 14.3.8.5.6b]). Participants in the DP arm with pre-existing renal insufficiency had a moderately higher incidence of thromboembolic events (10.5% [Table 14.3.8.5.7]) than participants without pre-existing renal insufficiency (4.9% [Table 14.3.8.5.7b]). As discussed in the initial response document, the incidence of thromboembolic events in participants with pre-existing renal insufficiency was comparable between the DP (10.5%) and BSC (12.0%) arms (Table 14.3.8.5.7).

A meaningful comparison of the safety of defibrotide in pediatric participants with and without pre-existing renal insufficiency is limited as only 4 pediatric participants had pre-existing renal insufficiency during the prophylaxis phase.

Of the 25 participants from the DP arm who were included in the rescue phase, only 3 had pre-existing renal insufficiency (Table 14.3.8.5.1). This precludes the analysis of safety for this small subpopulation during this phase of the study.

For participants in the DP arm with and without pre-existing renal insufficiency, Table 14.3.8.1.1a and Table 14.3.8.1.1b, respectively, provide summaries of vital signs for baseline and Day +30 post-HSCT, with changes from baseline to Day +30 post-HSCT. Similarly, Table 14.3.8.1.2a and Table 14.3.8.1.2b provide summaries of vital signs for participants with and without pre-existing renal insufficiency, respectively, at the time of diagnosis of VOD and Day +30 post-VOD treatment, with changes from VOD diagnosis to Day +30 post-VOD rescue treatment.

For participants in the DP arm with and without pre-existing renal insufficiency, respective summaries at baseline, at Day +30 post-HSCT, and with changes from baseline to Day +30 Post-HSCT are provided for hematology (Table 14.3.8.2.1a and Table 14.3.8.2.1b), chemistry (Table 14.3.8.3.1a and Table 14.3.8.3.1b), and coagulation (Table 14.3.8.4.1a and Table 14.3.8.4.1b) laboratory results. For participants in the DP arm with and without pre-existing renal insufficiency, respective summaries at the time of diagnosis of VOD, at Day +30 post-VOD treatment, and with changes from VOD diagnosis to Day +30 Post-VOD rescue treatment are provided for hematology (Table 14.3.8.2.2a and Table 14.3.8.2.2b), chemistry (Table 14.3.8.3.2a and Table 14.3.8.3.2b), and coagulation (Table 14.3.8.4.2a and Table 14.3.8.4.2b) laboratory results.

Although some substantial changes in laboratory values and vital signs from baseline to Day +30 post-HSCT and from VOD diagnosis to Day +30 post-VOD rescue treatment were observed between the subpopulations of participants with and without pre-existing renal insufficiency in the DP arm, the results should be interpreted with caution as the numbers of participants with pre-existing renal insufficiency are small, and smaller yet for those with laboratory values and vital signs captured at both time points analyzed.

Hypertension

Among participants with pre-existing renal insufficiency, hypertension was reported during the prophylaxis phase in a higher percentage of participants in the DP arm (11/19 [57.9%]) compared with the BSC arm (5/25 [20.0%]; Table 14.3.8.5.1). The percentage of participants in the DP arm that reported hypertension during the prophylaxis phase was also higher (although the difference was smaller) in participants with pre-existing renal insufficiency (57.9%) compared with participants

without pre-existing renal insufficiency (35.3% [Table 14.3.8.5.1b]). Renal disease and hypertension are often closely linked disorders in which one can be a precursor for the other. Frequent changes in blood pressure are also common in patients undergoing HSCT given their increased risk for infections, organ dysfunction, and other complications.

For the 11 participants in the DP arm with pre-existing renal insufficiency who experienced hypertension event(s), the majority of events were of Grade ≤ 2, and all cases were considered nonserious and unrelated to study treatment (Listing 6; Module 5.3.5.4/JZP15-007 CSR/Section 10.7/Listing 16.2.10.1). None of the hypertension events led to any action being taken with the study drug.

For participants in the DP arm with pre-existing renal insufficiency, the baseline mean and median systolic (113.3 mmHg and 111.0 mmHg, respectively) and diastolic pressures (68.0 mmHg and 68.5 mmHg, respectively) were within normal parameters (Table 14.3.8.1.1a). The mean and median changes from baseline to Day +30 Post-HSCT in systolic pressure were small (5.1 mmHg and 2.0 mmHg, respectively), and these values remained within normal parameters. Similarly, the mean and median changes in diastolic pressure were small (3.7 mmHg and 6.0 mmHg, respectively) and remained within normal parameters.

For the participants with pre-existing renal insufficiency, a summary of shift changes (low, normal, and high) for systolic and diastolic blood pressure values from baseline to each assessment (Table 14.3.3.3a), as well as a summary of maximum increases/decreases from baseline in systolic and diastolic blood pressure (Table 14.3.3.2a) were prepared. Most participants with pre-existing renal insufficiency in either treatment arm had normal blood pressure values at baseline, and values remained normal throughout the study. For this same subpopulation, the mean and median maximum increase in systolic and diastolic blood pressures were similar for the 2 treatment arms during the prophylaxis phase.

Given the very small population of participants with pre-existing renal insufficiency, limited data are available to support any conclusion regarding a causal association between defibrotide treatment and the higher incidence of hypertension TEAEs in this subpopulation of participants in the DP arm compared with the BSC arm. Given the co-morbidities and complications seen in patients undergoing HSCT, frequent changes in blood pressure are expected in this population.

Hypomagnesaemia

Among participants with pre-existing renal insufficiency, hypomagnesaemia was reported during the prophylaxis phase in a higher percentage of participants in the DP arm (36.8%) compared with the BSC arm (16.0%; Table 14.3.8.5.1). The percentage of participants in the DP arm that reported hypomagnesaemia during the prophylaxis phase was similar in participants with pre-existing renal insufficiency (36.8%) compared with participants without pre-existing renal insufficiency (39.5% [Table 14.3.8.5.1b]). For participants in the DP arm with pre-existing renal insufficiency, all reports of hypomagnesaemia were nonserious, of Grade ≤ 2, and considered unrelated to study treatment (Module 5.3.5.4/JZP15-007 CSR/Section 10.7/Listing 16.2.10.1). None of the hypomagnesaemia events led to any action being taken with the study drug.

While there was a difference in the reported incidence of hypomagnesaemia TEAEs, the percentage of participants with abnormally low laboratory values for blood magnesium levels during the study was similar between participants with pre-existing renal insufficiency in the DP and BSC arms, regardless of being captured as a TEAE per investigator decision (refer to laboratory shift tables: Table 14.3.8.7.1 and Table 14.3.8.7.2). Of participants with an available baseline value for blood magnesium, 91.7% (22/24) participants in the DP arm and 94.4% (17/18) participants in the BSC had an abnormally low blood magnesium level during the prophylaxis phase of the study.

There was only a moderate difference in the incidence of hypomagnesaemia between the overall safety population in DP arm and BSC arm (39.2% vs 33.3%, respectively [Module 5.3.5.4/JZP15-007 CSR/Table 14.3.1.4]). The percentage of participants with hypomagnesaemia reported as a TEAE was actually numerically lower than the overall population, but similar in participants with pre-existing renal insufficiency than without pre-existing renal insufficiency (36.8% vs 39.5%, respectively) in the DP arm (Table 13).

Overall, there is insufficient data for participants with pre-existing renal insufficiency from Study 15-007 to support a causal association between defibrotide treatment and the higher incidence of hypomagnesaemia TEAEs observed in the DP arm compared with the BSC arm. In general, a high incidence of electrolyte abnormalities (in particular low electrolyte levels) is expected in patients undergoing HSCT. There are multiple pathophysiologic explanations for this observation, including but not limited to gastrointestinal symptoms leading to electrolyte loss, renal disease, abnormal bone metabolism, and the engraftment itself, leading to intracellular uptake of electrolytes. In one retrospective study of 48 patients who underwent autologous HSCT, high incidences of electrolyte abnormalities were observed: hypokalaemia, 81% (39/48), hypomagnesaemia, 67% (32/48), hypocalcaemia, 49% (17/35) and hypophosphataemia, 91% (39/43) (Philibert, 2008). The incidence of low electrolyte levels in Study 15-007 is consistent with the published incidence for similar populations.

Hypokalaemia in Pediatric Participants

Among participants with pre-existing renal insufficiency, hypokalaemia was observed in 3 of 4 pediatric participants in the DP arm and 0 of the 4 pediatric participants in the BSC arm during the prophylaxis phase (Table 14.3.8.5.1). Hypokalaemia was a very common TEAE in the 95 pediatric participants without pre-existing renal disease in the DP arm and was reported in 40.1% of these participants during the prophylaxis phase. For participants in the DP arm without pre-existing renal insufficiency, the incidence of hypokalemia was also modestly higher for pediatric participants (42.1%) compared with adult participants (37.3%; Table 14.3.8.5.1b).

The pediatric participants with pre-existing renal insufficiency in the DP arm who reported hypokalaemia included younger participants ≤ 6 years of age. All hypokalaemia events in these pediatric participants were nonserious adverse events, and all were considered unrelated to study drug (Module 5.3.5.4/JZP15-007 CSR/Section 10.7/Listing 16.2.10.1). No action was taken with the study drug due to any of the hypokalaemia events. In all but one case, hypokalaemia resolved within 2 days of onset; the remaining event resolved 38 days after onset. In each participant, there were multiple factors that likely contributed to these episodes of hypokalaemia.

• Participant 1202-1002 was a 3-year-old male who experienced 5 separate TEAEs of hypokalaemia; 3 of which, were Grade 2 in severity and 2 events that were Grade 3 in severity. This participant was on the concomitant medication of furosemide (Module 5.3.5.4/JZP15-007 CSR/Section 10.4/Listing 16.2.6.2), a diuretic, which is frequently associated with hypokalaemia. His serum creatinine levels fluctuated during Study 15-007 (Module 5.3.5.4/JZP15-007 CSR/Section 10.8/Listing 16.2.11.2.1), and he experienced a nonserious TEAE of acute kidney injury.

• Participant 3206-1002 was a 6-year-old female who experienced 1 event of hypokalaemia, Grade 2 in severity. She was on the concomitant medication of furosemide.

• Participant 9707-1003 was a 16-month-old female who experienced 1 event of hypokalaemia, Grade 2 in severity. She was on the concomitant medication of furosemide. In addition, she experienced several concurrent nonserious gastrointestinal TEAEs (including vomiting and diarrhoea), which may have contributed to electrolyte imbalances.

While there was a difference in the reported incidence of hypokalaemia TEAEs, the percentage of pediatric participants with abnormally low laboratory values for blood potassium levels during the study was similar between participants with pre-existing renal insufficiency in the DP and BSC arms, regardless of being captured as a TEAE per investigator decision (refer to laboratory shift tables: Table 14.3.8.7.1a and Table 14.3.8.7.2a). Of pediatric participants with an available baseline value for blood potassium, 75.0% (3/4) in the DP arm and 50% (2/4) in the BSC arm had an abnormally low blood potassium level during the prophylaxis phase of the study.

Overall, hypokalaemia was a very commonly-reported TEAE during the prophylaxis phase with 39.2% participants in the DP and 33.3% in the BSC arms reporting this event (Module 5.3.5.4/JZP15-007 CSR/Table 14.3.1.4), representative of the incidence in this population. Given the very small population of pediatric participants with pre-existing renal insufficiency limited data are available to support any conclusion regarding a causal association between defibrotide treatment and hypokalaemia. The incidence of low electrolyte abnormalities in Study 15-007 was consistent with that in the literature for patients undergoing HSCT.

Summary of Safety in Participants with Pre-existing Renal Insufficiency

In this study, the safety of defibrotide in participants with pre-existing renal insufficiency was consistent with the known safety profile of defibrotide and with events commonly experienced in the study population. While the safety analyses were limited by the small number of participants with pre-existing renal insufficiency compared with the total safety population in the DP arm, no new safety signals were detected.

References

Philibert D, Desmeules S, Filion A, et al. Incidence and severity of early electrolyte abnormalities following autologous haematopoietic stem cell transplantation. Nephrology Dialysis Transplantation. 2008 Jan 1;23(1):359-63.

Assessment of the MAH's response

Overall, it is somewhat reassuring that serious TEAEs were reported in a higher proportion of participants in the defibrotide group without pre-existing renal insufficiency than with pre-existing renal insufficiency in the prophylaxis phase, and that no specific PT was reported as a serious event in more than 2 participants with pre-existing renal insufficiency. However, the number of participants with pre-existing renal insufficiency was low, and a higher proportion of bleeding events was reported in participants with pre-existing renal insufficiency (57.9%) as compared to those without (46.3%).

Based on the presentation of data on changes in laboratory values and vital signs from baseline to Day +30 post-HSCT (and from VOD diagnosis to Day +30 post-VOD rescue treatment) in patients with and without renal insufficiency in the defibrotide group, no conclusions can be made.

For hypertension among patients with renal insufficiency, the MAH has provided data on the change in mean and median systolic and diastolic pressures from baseline to Day +30 post-HSCT in the defibrotide group, with an increase in systolic pressure of mean 5.1 mmHg and median 2.0 mmHg, and an increase in diastolic pressure in mean 3.7 mmHg and median 6.0 mmHg. These changes are considered small and of unclear clinical significance given that they are based on a low number of subjects. Of note, hypertension was reported during the prophylaxis phase of study 15-007 in a higher proportion of participants in the defibrotide arm (11/19 [57.9%]) compared with the best supportive care arm (5/25 [20.0%]); however, this is contrasted with a statement that most participants with pre-existing renal insufficiency in either treatment arm had normal blood pressure values at baseline, and values remained normal throughout the study. It is noted that mean and median systolic blood

pressure values were lower in the defibrotide group as compared to the best supportive care group at baseline (median 111.0 mmHg and 123.5 mmHg respectively) and similar, for diastolic blood pressure, median was 68.5 mmHg in the defibrotide group and 77.0 mmHg in the best supportive care group. Thus, despite a lower blood pressure at baseline in patients with pre-existing renal insufficiency, more patients in the defibrotide group were reported to have hypertension during the prophylaxis phase. However, the reported events of hypertension appear not to be related to any clinically significant increase in blood pressure at Day +30 post-HSCT.

For hypomagnesaemia, there was a higher proportion of patients with pre-existing renal insufficiency during the prophylaxis phase in the defibrotide arm as compared to best supportive care. However, there was no difference between patients with and without pre-existing renal insufficiency based on reported hypomagnesaemia in the defibrotide arm, and there was no difference in proportion of patients with low blood magnesium levels (based on laboratory values instead of reported TEAEs) between the two treatment arms among those with an available magnesium value at baseline. No conclusions can be made.

For hypokalaemia, it is unclear why the response has focused on the paediatric population only, with numerically very few events. No conclusions can be made.

Overall, no firm conclusions on the safety of defibrotide in patients with pre-existing renal insufficiency can be made. Despite the MAH responses not being satisfactory, it is not likely that additional analyses will be of value.

Conclusion

Issue not further pursued.

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

Question 7. For participants with pre-existing intrinsic lung disease at baseline in study 15-007, the MAH is asked to discuss the safety findings in relation to the overall safety population.

Summary of the MAH's response

The MAH previously provided safety analyses for participants with pre-existing intrinsic lung disease by treatment arm for the overall safety population of Study 15-007 and for pediatric and adult participants. To supplement the prior comparison, additional safety analyses were performed to compare the safety profile of defibrotide in participants randomized to the defibrotide prophylaxis (DP) arm who had pre-existing intrinsic lung disease to those without pre-existing intrinsic lung disease. This comparison provides an assessment of the impact of participants with pre-existing intrinsic lung disease on the overall safety population. As in the previously-submitted analyses, a participant was determined to have pre-existing intrinsic lung disease if they had any medical condition at baseline within the High Level Group Terms (HLGTs) of bronchial disorders (excl neoplasms), congenital respiratory tract disorders, lower respiratory tract disorders (excl obstruction and infection), neonatal respiratory disorders, respiratory disorders NEC, and respiratory tract neoplasms. Baseline was defined in the Study 15-007 protocol as the day before conditioning begins for participants in the DP arm, and on the day that conditioning begins for participants in the best supportive care (BSC) arm.

<u>Comparison of Participants with Pre-existing Intrinsic Lung Disease to those without Pre-existing Intrinsic Lung Disease in the DP arm – Prophylaxis Phase</u>

During the prophylaxis phase of Study 15-007, only a small number of participants in the DP arm were identified as having pre-existing intrinsic lung disease at baseline (n=8 [Table 14.3.9.5.1]) compared

with the number of participants without pre-existing intrinsic lung disease in the DP arm (n=173 [Table 14.3.9.5.1b]). More pediatric participant (n=7) had pre-existing intrinsic lung disease compared to adults (n=1); whereas, the number of participants in the DP arm without pre-existing intrinsic lung disease was similar for pediatric (n=92) and adult (n=81) participants. The types of pre-existing intrinsic lung disease seen in the DP arm included peripheral oedema (in 2 participants) and interstitial lung disease, lung consolidation, lung disorder, metastases to lung, pulmonary mass/respiratory distress, and respiratory acidosis (1 participant each). The types of pre-existing intrinsic lung disease seen in the BSC arm included pulmonary mass (in 3 participants), lung disorder and respiratory failure (2 participants each), and chronic obstructive pulmonary disease and restrictive pulmonary disease (1 participant each) (Table 14.1.6b). A comparison of safety data for participants with pre-existing intrinsic lung disease to those without pre-existing lung disease was limited due to the very small numbers of such participants in Study 15-007. Participants with pre-existing lung disease represented only 4.4% (8/181) of the safety population in the DP arm. During the prophylaxis phase, for participants in the DP arm with pre-existing intrinsic lung disease, the most commonly reported TEAE by preferred terms (PTs) included hypokalaemia, pyrexia, anaemia, neutropenia, and hypomagnesaemia (Table 14). For participants in the DP arm without pre-existing intrinsic lung disease, the most commonly reported treatment-emergent adverse event (TEAE) by PTs included nausea, pyrexia, diarrhoea, stomatitis, and vomiting. The small size of the population of participants with pre-existing lung disease prevents the meaningful identification of any trends and for any conclusions to be made.

Table 14: Treatment-Emergent Adverse Events ≥ 25% in Participants in the DP arm With or Without Pre-existing Intrinsic Lung Disease (Study 15-007 Prophylaxis Phase; Safety Analysis Set)

	Participants with Pre-Existing Intrinsic Lung Disease			Participants without Pre-Existing Intrinsic Lung Disease		
Preferred Term (MedDRA)	**Total n=8**	**Pediatric (≤16 yr) n=7**	**Adult (>16 yr) n=1**	**Total n=173**	**Pediatric (≤16 yr) n=92**	**Adult (>16 yr) n=81**
Number of Participants With at Least 1 TEAE, n (%)	**8 (100)**	**7 (100)**	**1 (100)**	**172 (99.4)**	**92 (100)**	**80 (98.8)**
Hypokalaemia	6 (75.0)	5 (71.4)	1 (100)	65 (37.6)	38 (41.3)	27 (33.3)
Pyrexia	5 (62.5)	4 (57.1)	1 (100)	106 (61.3)	64 (69.6)	42 (51.9)
Anaemia	4 (50.0)	3 (42.9)	1 (100)	44 (25.4)	26 (28.3)	18 (22.2)
Hypomagnesaemia	4 (50.0)	3 (42.9)	1 (100)	67 (38.7)	44 (47.8)	23 (28.4)
Neutropenia	4 (50.0)	3 (42.9)	1 (100)	27 (15.6)	16 (17.4)	11 (13.6)
Diarrhoea	3 (37.5)	2 (28.6)	1 (100)	102 (59.0)	49 (53.3)	53 (65.4)
Febrile neutropenia	3 (37.5)	3 (42.9)	0	49 (28.3)	33 (35.9)	16 (19.8)
Hypophosphataemia	3 (37.5)	2 (28.6)	1 (100)	16 (9.2)	11 (12.0)	5 (6.2)
Nausea	3 (37.5)	2 (28.6)	1 (100)	106 (61.3)	55 (59.8)	51 (63.0)
Stomatitis	3 (37.5)	3 (42.9)	0	102 (59.0)	59 (64.1)	43 (53.1)
Acute graft versus host disease in skin	2 (25.0)	1 (14.3)	1 (100)	28 (16.2)	9 (9.8)	19 (23.5)
Alopecia	2 (25.0)	2 (28.6)	0	5 (2.9)	3 (3.3)	2 (2.5)
Constipation	2 (25.0)	1 (14.3)	1 (100)	32 (18.5)	13 (14.1)	19 (23.5)
Cytomegalovirus infection	2 (25.0)	1 (14.3)	1 (100)	22 (12.7)	10 (10.9)	12 (14.8)
Decreased appetite	2 (25.0)	2 (28.6)	0	48 (27.7)	23 (25.0)	25 (30.9)
Epistaxis	2 (25.0)	2 (28.6)	0	37 (21.4)	19 (20.7)	18 (22.2)
Hyperglycaemia	2 (25.0)	2 (28.6)	0	19 (11.0)	7 (7.6)	12 (14.8)
Hypertension	2 (25.0)	1 (14.3)	1 (100)	66 (38.2)	33 (35.9)	33 (40.7)

	Participants with Pre-Existing Intrinsic Lung Disease			Participants without Pre-Existing Intrinsic Lung Disease		
Preferred Term (MedDRA)	Total n=8	Pediatric (≤16 yr) n=7	Adult (>16 yr) n=1	Total n=173	Pediatric (≤16 yr) n=92	Adult (>16 yr) n=81
Hypoalbuminaemia	2 (25.0)	2 (28.6)	0	25 (14.5)	15 (16.3)	10 (12.3)
Hyponatraemia	2 (25.0)	1 (14.3)	1 (100)	13 (7.5)	7 (7.6)	6 (7.4)
Oedema peripheral	2 (25.0)	2 (28.6)	0	24 (13.9)	10 (10.9)	14 (17.3)
Oral candidiasis	2 (25.0)	1 (14.3)	1 (100)	6 (3.5)	4 (4.3)	2 (2.5)
Pain	2 (25.0)	2 (28.6)	0	18 (10.4)	14 (15.2)	4 (4.9)
Pain in extremity	2 (25.0)	2 (28.6)	0	16 (9.2)	9 (9.8)	7 (8.6)
Thrombocytopenia	2 (25.0)	1 (14.3)	1 (100)	29 (16.8)	13 (14.1)	16 (19.8)
Urticaria	2 (25.0)	2 (28.6)	0	7 (4.0)	3 (3.3)	4 (4.9)
Vomiting	2 (25.0)	1 (14.3)	1 (100)	101 (58.4)	63 (68.5)	38 (46.9)
Weight increased	2 (25.0)	2 (28.6)	0	20 (11.6)	9 (9.8)	11 (13.6)
Abdominal pain	1 (12.5)	1 (14.3)	0	56 (32.4)	33 (35.9)	23 (28.4)
Headache	1 (12.5)	1 (14.3)	0	48 (27.7)	14 (15.2)	34 (42.0)

Abbreviations: DP=defibrotide prophylaxis; MedDRA=Medical Dictionary for Regulatory Activities; TEAE=treatment-emergent adverse event.
Source: Table 14.3.9.5.1, Table 14.3.9.5.1b

During the prophylaxis phase, participants with and without pre-existing intrinsic lung disease reported a similar incidence of serious TEAEs (50.0% vs 40.5%, respectively [Table 14.3.9.5.2 and Table 14.3.9.5.2b]) and treatment-related TEAEs (25% vs 22.5%, respectively [Table 14.3.9.5.3 and Table 14.3.9.5.3b]). No TEAE by PT was reported as serious in more than 1 participant with pre-existing intrinsic lung disease in the DP arm. Treatment-related TEAEs were reported in 2 participants with pre-existing intrinsic lung disease in the DP arm; events included cerebral haemorrhage and haemoptysis. The majority of treatment-related TEAEs in participants without pre-existing intrinsic lung disease were also related to bleeding events. These results are consistent with the known safety profile of defibrotide. During the prophylaxis phase, there were no participants with pre-existing intrinsic lung disease who experienced a fatal TEAE (Table14.3.9.5.5) compared to 5.8% of participants without pre-existing intrinsic lung disease (Table14.3.9.5.5b).

Overall, bleeding events were reported in a higher percentage of participants with pre-existing intrinsic lung disease (6/8 [75%]; Table 14.3.9.5.6) than those without (80/173 [46.2%]; Table 14.3.9.5.6b). There were no thromboembolic events reported in participants with pre-existing intrinsic lung disease (Table 14.3.9.5.7), while such events were reported in 5.8% of participants without pre-existing intrinsic lung disease in the DP arm (Table 14.3.9.5.7b).

Comparison of Participants in the DP arm with Pre-existing Intrinsic Lung Disease to those without Pre-existing Intrinsic Lung Disease – Rescue Phase: A comparison of the safety results for participants in DP arm with and without pre-existing intrinsic lung disease was not possible during the rescue phase, since only 1 of 25 participants was identified as having pre-existing intrinsic lung disease (Table 14.3.9.5.1).

Comparison of Participants in the DP arm with Pre-existing Intrinsic Lung Disease to those without Pre-existing Intrinsic Lung Disease – Vital Signs & Laboratory Results

For participants in the DP arm with and without pre-existing intrinsic lung disease, Table 14.3.9.1.1a and Table 14.3.9.1.1b, respectively, provide summaries of vital signs for baseline and Day +30 post-HSCT, with changes from baseline to Day +30 post-HSCT. Similarly, Table 14.3.9.1.2a and Table 14.3.9.1.2b provide summaries of vital signs for participants with and without pre-existing intrinsic lung disease, respectively, at the time of diagnosis of VOD and Day +30 post-VOD rescue treatment with changes from VOD diagnosis to Day +30 post-VOD rescue treatment.

For participants in the DP arm with and without pre-existing intrinsic lung disease, respective summaries at baseline, at Day +30 post-HSCT, and with changes from baseline to Day +30 Post-HSCT are provided for hematology (Table 14.3.9.2.1a and Table 14.3.9.2.1b), chemistry (Table 14.3.9.3.1a and Table 14.3.9.3.1b), and coagulation (Table 14.3.9.4.1a and Table 14.3.9.4.1b) laboratory results. For participants in the DP arm with and without pre-existing intrinsic lung disease, respective summaries at the time of diagnosis of VOD, at Day +30 post-VOD rescue treatment, and with changes from VOD diagnosis to Day +30 Post-VOD rescue treatment are provided for hematology (Table 14.3.9.2.2a and Table 14.3.9.2.2b), chemistry (Table 14.3.9.3.2a and Table 14.3.9.3.2b), and coagulation (Table 14.3.9.4.2a and Table 14.3.9.4.2b) laboratory results.

Although some substantial changes in laboratory values and vital signs from baseline to Day +30 post-HSCT and from VOD diagnosis to Day +30 post-VOD rescue treatment were observed between the subpopulations of participants with and without pre-existing intrinsic lung disease in the DP arm, the results should be interpreted with caution as the numbers of participants with pre-existing intrinsic lung disease were very small, and smaller yet for those with laboratory values and vital signs captured at both time points analyzed.

Summary of Safety in Participants with Pre-existing Intrinsic Lung Disease

While very few participants with pre-existing intrinsic lung disease received defibrotide in this study limiting any comparisons of safety to participants without pre-existing lung disease, no new safety signals for defibrotide were detected.

Assessment of the MAH's response
The MAH has provided the requested analyses. Due to the low number of patients in the defibrotide prophylaxis arm who had pre-existing lung disease at baseline, no firm conclusions can be drawn, however, based on the data provided, there are no unexpected safety findings.

Conclusion

Issue resolved.

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

SmPC

Question 8. SmPC comments.

Summary of the MAH's response
See attached SmPC with comments.

Assessment of the MAH's response
Additional amendments of section 5.1 are requested; see attached SmPC with comments.

Conclusion

Issue not resolved.

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

15. 3rd Request for supplementary information

15.1. Other concerns

Safety / RMP

Given the clear lack of benefit shown in this study, the well documented off label use in the prophylactic setting (See also EMEA/H/C/002393/II/0058) raises substantial concerns, as the safety profile of this product is not benign. It is therefore considered important to communicate directly to concerned health care professionals about these new data. The MAH is asked to submit a draft for a Direct Healthcare Professionals Communication (DHPC) together with a draft Communication plan (see also GVP Module XV – Safety communication including Annex II with templates for the DHPC and Communication plan). The key points to address include the main efficacy results in the prophylactic setting together with a summary of the main safety problems with the product.

SmPC

1. See attached SmPC with comments.

16. Assessment of the responses to the 3nd request for supplementary information

Q1 Safety / RMP

Request for DHPC

Summary of the MAH's response

The MAH acknowledges the request from EMA and appreciates the expeditious review. We would like to provide the following clarification in response to this request and highlight that additional Direct Healthcare Professional (DHPC) communication would be unnecessary as the overall benefit-risk balance of defibrotide remains unchanged.

The MAH would like to highlight that no new safety concerns from the study have been raised, as agreed by the EMA in the assessment report "For the safety concerns addressed by this study, overall, no firm conclusions can be drawn; however, no new safety concerns have been identified". The safety profile of defibrotide from the clinical development programme and post marketing use globally (>15000 patients) has also been shown to remain positive as reflected in the PRAC approved PBRER reports. This provides extensive evidence on the favourable benefit-risk balance of defibrotide in the approved indication. The MAH is concerned that since DHPC letters are sent out when there is a clear new safety signal, a DHPC communication additional to the communication (as described below) already implemented by the MAH may create confusion among HCPs on the use of defibrotide also in the approved indication. This in-turn may risk patient best care management.

In addition, the MAH has made changes to the SmPC (as per EMA request) and implemented an extensive global communication plan communicating the results (efficacy and safety) from study 15-007 to Healthcare Professionals globally both directly and publicly.

The global communication plan, regarding study 15-007 futility (not meeting the primary endpoint of the study) and summary of the efficacy and safety results, included the following:

- A press release worldwide following the Interim analysis on 29 April 2020 (copy enclosed). Direct communication and presentation of the final study results (efficacy and safety) to all 140

study sites (including PI and site study team), regardless of the site enrolment status, globally. This personal communication comprised of three Virtual Zoom regional meetings (US, EU/Israel and Middle East and APAC) held on 29 April 2021. The 140 study sites are comprised of transplant centres in Europe and globally that perform at least 100 transplants annually.

- The final study results have been published on global Health Authority clinical trial websites (including but not limited to EudraCT, Clintrials.gov).
- In addition, the final efficacy and safety results have been presented at international congresses

(ASH 2021 and EBMT 2022) with extensive presence of transplant physicians from Europe and worldwide. A full manuscript is also being prepared for publication in peer reviewed scientific journals.

Importantly, it is not common regulatory practice to provide a DHPC to proactively address an off-label indication, especially in the absence of a clear new safety signal and would represent a significant regulatory shift in purpose and management of communications to HCPs. DHPC are typically used to highlight safety risks for an approved indication, and not to address unmet efficacy results from a study investigating an unapproved indication where no new safety concerns were found. The guidance and EMA DHPC template are specifically for safety concerns (GVP Module XV – Safety communication including Annex II with templates for the DHPC and Communication plan), which is not the case here for defibrotide.

The MAH would like to emphasize that the use of defibrotide off-label is not promoted by Jazz and is entirely at the discretion of the treating HCP, as the case with many other products, and is out of control of the MAH. The MAH has no direct means of measuring and monitoring off label use. However, enrolment data from DefiFrance showed a decline in the number of patients who received defibrotide prophylaxis over the previous years.

Of note, as part of commitments by the MAH and in compliance with regulatory requirements, study 15- 007 results and the final CSR were also submitted to other global regulatory authorities and Post-Marketing Requirements (PMR) closure approved.

Given the above, we hope that the PRAC and CHMP Rapporteur agree that additional DHPC communication is unwarranted. We also hope that the EMA agree that the communication plan already implemented by the MAH in sharing the results from the 15-007 study has been sufficiently comprehensive, and that the overall benefit-risk profile of the drug remains unchanged as no new safety signals have been identified as part of this study. As the MAH, we confirm our commitment to continued monitoring of safety of defibrotide within the EU and globally with the ultimate aim of helping to improve patients' best care management.

PRAC Rapp's comment:

The MAH is reluctant to send out a DHPC as there is no new safety signal changing the overall B/R. In this case however, the rational for the DHPC is to avoid exposure (and thus possibly severe adverse events) in a population where lack of efficacy has been shown. The efforts made by the MAH to present data from the study is acknowledged. Nevertheless, as shown in DefiFrance (see EMEA/H/C/002393/II/0058) the off label use for prevention has been extensive with a large number of patients at risk for adverse events without anticipated benefit of use it is important that the information is distributed to all concerned bodies not only the academic community and study centres.

Thus a DHPC with a communication plan is still requested. The comments from PRAC (See section 9 and attachments) should be taken onboard (**LoOI**).

Issue not resolved.

Q2 SmPC Section 5.1

Summary of the MAH's response

The MAH acknowledges and accepts all of the changes made by the authorities but has made slight amendments as followed:

1. In the last paragraph prior to the paediatric population subsection in 5.1 of the SmPC the MAH has rejected the deletion of "During prophylaxis" and re-introduced this into the label. Per responses provided in sequence 0132 this paragraph presents data from the prophylaxis phase of the study and therefore this should be explicitly stated to ensure the context of the information is interpreted correctly.

2. In the same paragraph prior to the paediatric population subsection in 5.1 of the SmPC the MaH acknowledges the comment by the authorities related to overall mortality and has accept the new wording describing mortality at day +30. The MAH however has rejected the deletion of data presenting fatalities related to TEAEs "...,and fatal TEAEs (5.5% vs 5.7%, respectively)". This data again provides more context for prophylaxis phase of the study, further is more clinically relevant to clinicians. With the addition of the new proposed wording for deaths at day+30 post HSCT this should provide a balanced presentation of the relevant data from the study.

3. In the paediatric population subsection of 5.1 in the SmPC the MAH acknowledges the rationale by the authorities to not mix the populations of prophylaxis and treatment. The MAH however believes the number of paediatric patients provides valuable context to clinicians considering the rare nature of the disease VOD and the limited availability of paediatric data in general. The MAH has therefore included the figure of ped patients from the three treatment studies only: Subjects <18 years who received Defitelio at the 25 mg/kg/day dose level.

PRAC Rapp's comment:

Most concerns raised in the last round of assessment are addressed but there are three points where the PRAC's proposal was not implemented.

Re point 1 above: The whole context is about study 15-007 and thus it appears confusing rather than clarifying to repeat the information about prophylactic use when presenting data on adverse events. For clarity the study could be presented in one single paragraph instead of split in three.

Re point 2: It is not acceptable to retain this text. The data to be presented is the number of deaths as now included (and which the MAH accepts to retain) and it would be confusing to add in addition numbers of fatal events as these numbers differs. It is not agreed that the latter would be more relevant for the prescribers, rather the contrary.

Re point 3: The inclusion of the number of paediatric subjects treated is accepted. However, the text in brackets should be moved to avoid misinterpretation.

Thus, further updates to the SmPC are warranted (**LoOI**)

Issue partly resolved.

17. 4rd Request for supplementary information

RMP

The MAH is asked to submit a draft for a Direct Healthcare Professionals Communication (DHPC) together with a draft Communication plan (see also GVP Module XV – Safety communication including Annex II with templates for the DHPC and Communication plan). The key points to address include the main efficacy results in the prophylactic setting together with a summary of the main safety problems with the product. The comments from the PRAC at its meeting on 2-5 May, should be taken onboard.

SmPC

Please see appended SmPC.

18. Responses to the 4rd Request for supplementary information

RMP

The MAH provided a draft DHPC with communication plan which was assessed and found not acceptable at the PRAC May meeting. Following up to this PRAC drafted a proposal which was accepted by the MAH with some proposals for minor amendments. This text (entitled: *Defitelio (defibrotide): Not recommended for prophylaxis of veno-occlusive disease (VOD) after post-hematopoietic stem-cell transplantation (HSCT)* is deemed acceptable.

Issue resolved.

SmPC

The MAH has submitted an updated SmPC revised as requested by CHMP. A few additional editorial changes were made, which are all acceptable. Nevertheless, the version of the SmPC submitted did not include the update of Annex E agreed in procedure EMEA/H/C/002393/S/0057. Whereas study 15-007 (subjected to the present procedure) is accurately no longer listed as a specific obligation, the new measure (*In order to further characterise the efficacy and safety of Defitelio in the treatment of severe hepatic veno-occlusive disease, the MAH should provide yearly updates on any new information concerning the safety and efficacy of Defitelio*) is not included.

The company has provided an updated PI to list the new specific obligation as agreed in the annual-reassessment procedure EMEA/H/C/002393/S/0057.

Issue resolved.

At the CHMP meeting in May 2022, the CHMP requested to the company to change the DHPC and communication plan: This text (entitled: *Defitelio (defibrotide): Dot not use for prophylaxis of veno-occlusive disease (VOD) after post-hematopoietic stem-cell transplantation (HSCT)*

This update was agreed with the MAH.