Defibrotide plus best standard of care compared with best standard of care alone for the prevention of sinusoidal obstruction syndrome (HARMONY): a randomised, multicentre, phase 3 trial

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Summary

Background Sinusoidal obstruction syndrome, also known as veno-occlusive disease, is a potentially life-threatening complication of haematopoietic stem-cell transplantation (HSCT). We aimed to compare defibrotide prophylaxis plus best supportive care versus best supportive care alone for sinusoidal obstruction syndrome prevention after HSCT.

Methods This open-label, randomised, multicentre, phase 3 trial was done in 104 centres in 14 countries. Patients who were at least 1 month old, were scheduled to receive allogeneic HSCT (adult [aged >16 years] or paediatric [aged >1 month to ≤16 years] patients) or autologous HSCT (paediatric patients only), and were at high risk or very high risk of developing sinusoidal obstruction syndrome were eligible for inclusion. Patients were randomly assigned (1:1) by an interactive web response system to receive intravenous defibrotide 25 mg/kg per day (four equal doses [6·25 mg/kg per dose]) and best supportive care (determined by individual institutional guidelines; defibrotide prophylaxis group) or best supportive care only (best supportive care group). Randomisation was stratified by sinusoidal obstruction syndrome risk, age, and country. The primary endpoint, sinusoidal obstruction syndrome-free survival at day 30 after HSCT, was assessed by an independent Endpoint Adjudication Committee in the intention-to-treat (ITT) population. Safety was assessed in all patients who received protocol treatment. The trial is registered with ClinicalTrials.gov, NCT02851407.

Findings Between Jan 11, 2017, and Oct 20, 2020, 372 patients (172 [46%] women and 200 [54%] men; median age 14·0 years [IQR 4·0–41·0] were randomly assigned to the defibrotide prophylaxis group (n=190) or best supportive care group (n=182; ITT population). On the basis of recommendations from the Independent Data Monitoring Committee following completion of the planned interim analysis in the first 280 recruited patients on April 29, 2020, enrolment was prematurely stopped for presumed futility. At the final analysis, sinusoidal obstruction syndrome-free survival by day 30 after HSCT was 67% (95% CI 58–74) in the defibrotide prophylaxis group and 73% (62–80) in the best supportive care group (HR 1·27 [95% CI 0·84–1·93]; p=0·85). Treatment-emergent adverse events were similar between groups during the randomised prophylaxis phase; most treatment-emergent adverse events were related to the transplantation rather than to study drug. The most common grade 3 or 4 treatment-emergent adverse events were stomatitis (grade 3, 52 [29%] of 181 patients in the defibrotide prophylaxis group and 56 [32%] of 174 patients in the best supportive care group; grade 4, two [1%] in the defibrotide prophylaxis group and two [1%] in the best supportive care group) and febrile neutropaenia (grade 3, 51 [28%] in the defibrotide prophylaxis group and 52 [30%] in the best supportive care group; grade 4, no patients in the defibrotide prophylaxis group and three [2%] in the best supportive care group). Serious treatment-emergent adverse events occurred in 74 (41%) of 181 patients in the defibrotide prophylaxis group and 61 (35%) of 174 patients in the best supportive care group. In the rescue phase, when patients in both treatment groups received defibrotide as rescue treatment, fatal treatment-related adverse events occurred in one (4%) of 25 patients in the defibrotide prophylaxis group (intracranial haemorrhage) and one (3%) of 31 patients in the best supportive care group (sinusoidal obstruction syndrome).

Interpretation Defibrotide did not show a benefit in the prophylaxis of sinusoidal obstruction syndrome. Additional studies of carefully selected patients at high risk of sinusoidal obstruction syndrome after HSCT are warranted.

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Research in context

Evidence before this study

We searched PubMed using the terms "veno-occlusive disease", "VOD", "sinusoidal obstruction syndrome", "SOS", "haematopoietic cell transplantation", "hematopoietic cell transplantation", "haematopoietic stem cell transplantation", and "hematopoietic stem cell transplantation" for articles published in any language between the inception of the database and May 9, 2016. We found a small number of controlled, peer-reviewed studies investigating defibrotide for the prophylaxis of sinusoidal obstruction syndrome after haematopoietic stem-cell transplantation (HSCT), highlighting the need for randomised, controlled clinical data in both paediatric and adult patients to determine the safety and efficacy of defibrotide for sinusoidal obstruction syndrome prophylaxis after HSCT.

Added value of this study

This trial represents the largest prospective, randomised, phase 3 study of defibrotide prophylaxis added to best supportive care compared with best supportive care alone for the prevention of sinusoidal obstruction syndrome in patients undergoing HSCT. The study's primary and key secondary endpoints were defined using sinusoidal obstruction syndrome evaluations by an independent masked Endpoint Adjudication Committee (EPAC) rather than by investigators who were involved in real-time bedside patient care. Although the trial was negative, discrepancies in assessment of sinusoidal obstruction syndrome between the independent adjudicators and the site investigators, even when using the same diagnostic criteria, highlight the challenges in diagnosing sinusoidal obstruction syndrome. Due to the inclusion of the best supportive care group, this large, randomised trial allowed evaluation of the safety profile of defibrotide versus best supportive care during the prophylactic treatment phase.

Implications of all the available evidence

Although this study was unsuccessful, previous clinical evidence had supported the use of defibrotide for the prophylaxis of sinusoidal obstruction syndrome in patients at a high risk of disease after HSCT. The observed discrepancies between EPAC and investigator assessments highlight the challenges involved in the diagnosis of this rare disease. Given the high mortality rate associated with sinusoidal obstruction syndrome, more studies on strategies to prevent development of the disease are warranted, especially in patients at high risk of disease.

Introduction

Haematopoietic stem-cell transplantation (HSCT) is a potentially curative therapy for many patients with haematological malignancies; however, conditioning regimens necessary to eradicate the underlying disease might cause endothelial cell activation and injury, resulting in sinusoidal obstruction syndrome, also referred to as veno-occlusive disease. Sinusoidal obstruction syndrome of the liver is a potentially life-threatening complication of HSCT.[1] The most severe form of the disease is associated with multiorgan dysfunction and failure and a mortality rate of more than 80% in untreated patients.[1] Risk factors for sinusoidal obstruction syndrome include very young age (<2 years), previous hepatic disease, previous treatment with gemtuzumab ozogamicin or inotuzumab ozogamicin, high-intensity or myeloablative conditioning regimens (in particular patients who received busulfan), and previous exposure to sirolimus.[2,3] Diseases particularly associated with severe sinusoidal obstruction syndrome after HSCT include haemophagocytic lymphohistiocytosis, thalassaemia with liver fibrosis, neuroblastoma, and osteopetrosis.[4] The incidence of sinusoidal obstruction syndrome after HSCT has been reported to be 60% in some very high-risk populations, but incidence of the disease is significantly influenced by patient characteristics, conditioning regimens, and transplantation type (allogeneic *vs* autologous; mismatched unrelated donors).[5]

Sinusoidal obstruction syndrome occurs as a result of activation and damage of the sinusoidal endothelium.[6–8] In the HSCT setting, endothelial damage initially caused by radiation or toxic metabolites of conditioning regimens can be exacerbated by proinflammatory and proapoptotic responses of the endothelial tissues.[8] The synthesis of clotting factors facilitates platelet aggregation, leading to a hypercoagulable state.[8] Defibrotide is approved for treatment of sinusoidal obstruction syndrome with renal or pulmonary dysfunction after HSCT in the USA[9] and severe hepatic sinusoidal obstruction syndrome after HSCT in patients older than 1 month in the EU;[10] however, it is not approved for the prophylaxis of sinusoidal obstruction syndrome after HSCT. In vitro, defibrotide has been shown to stabilise and protect endothelial cells through restoration of the thrombotic–fibrinolytic balance.[11]

Defibrotide also exerts anti-inflammatory and antioxidant effects and has antiapoptotic and antiangiogenic properties, suggesting potential use as a prophylactic drug for sinusoidal obstruction syndrome.[11] Several studies of defibrotide for sinusoidal obstruction syndrome prophylaxis in patients at high risk for the disease have been reported.[12–14] A large phase 3, prospective, randomised, controlled study (NCT00272948) in paediatric patients (<18 years) at high risk for the disease showed a lower incidence of sinusoidal obstruction syndrome at day 30 after HSCT with defibrotide prophylaxis (at 12%) versus control (no defibrotide; 20%).[12] A meta-analysis of more than 1000 patients from randomised, controlled trials and retrospective analyses suggested a reduction in the risk of sinusoidal obstruction syndrome for patients treated

with defibrotide prophylaxis versus controls (risk ratio 0·3 [95% CI 0·12–0·71]; p=0·006), suggesting a benefit of defibrotide prophylaxis.[13] A large, retrospective study (n=248) also supported a benefit of defibrotide prophylaxis versus control (no defibrotide) on the incidence of sinusoidal obstruction syndrome at day 100.[14]

We aimed to build on this existing evidence by assessing whether defibrotide would prevent sinusoidal obstruction syndrome in adult and paediatric patients who received HSCT and who were at a high or very high risk of sinusoidal obstruction syndrome.

Methods

Study design and participants

This global, open-label, randomised, multicentre, controlled, adaptive, phase 3 study, which compared the efficacy and safety of defibrotide plus best supportive care with best supportive care alone for prevention of sinusoidal obstruction syndrome in adult and paediatric patients undergoing HSCT who were at high or very high risk of developing sinusoidal obstruction syndrome, was done in 104 centres in 14 countries (appendix pp 1, 3–5). The study fulfilled a post-marketing requirement to collect data on the safety of defibrotide in a randomised setting.

Eligible patients were older than 1 month at the start of the study, were scheduled to receive allogeneic HSCT (adult [aged >16 years] or paediatric [aged >1 month to ≤16 years] patients) or autologous HSCT (paediatric patients only) and were at high risk or very high risk of developing sinusoidal obstruction syndrome (appendix p 2).

High-risk patients were defined as those who were scheduled to receive myeloablative conditioning therapy (either ≥2 alkylating drugs or total body radiation [single dose ≥5 Gy or ≥8 Gy fractionated dose] plus an alkylating drug) and had any hepatic risk factor as per the 2015 EBMT criteria[15] or had advanced-stage neuroblastoma requiring myeloablative conditioning. Patients at very high risk were defined as those who had osteopetrosis or primary immunodeficiency and needed myeloablative conditioning treatment, primary haemophagocytic lymphohistiocytosis, received previous treatment with an ozogamicin-containing regimen or class 3, high-risk thalassaemia and were ≥7 years old with a confirmed diagnosis of hepatomegaly. Patients with haemodynamic instability, clinically significant acute bleeding within 24 h before the start of treatment, or those taking any medication that increased risk of bleeding within 24 h before the start of study treatment were excluded. Patients with a psychiatric illness, patients (or representatives) deemed incapable of providing full consent, with a serious active disease or comorbid medical condition, and patients receiving or planning to receive alternative investigational therapies were also excluded. Female patients (and female partners of male patients) of childbearing potential who were sexually active were required to use a highly effective method of contraception. Post-menopausal female participants (ie, women with >2 years of amenorrhea) did not need to use contraception.

Clinical laboratory tests assessed at screening for eligibility included blood chemistry (for bilirubin [>1·5 times the upper limit of normal within 14 days of screening], hepatic function [transaminase >2·5 times upper limit of normal within 14 days of screening], and renal functions), serum ferritin for assessment of iron overload (serum ferritin >2000 ng/mL or liver iron content ≥5·0 mg/g dry weight as estimated by MRI T2* within 3 months before screening), and serological tests for hepatitis (hepatitis A virus immunoglobulin M; hepatitis B virus [HBV] core IgG or IgM; HBV surface antigen; HBV DNA by PCR or nucleic acid amplification testing; hepatitis C virus antibody or RNA by PCR or nucleic acid amplification testing).

Institutional review boards at participating centres approved the study, which was done in accordance with the Declaration of Helsinki and the Good Clinical Practice Guidelines of the International Conference on Harmonisation. All patients or their parents or legal guardians provided written informed consent.

See Online for appendix

Randomisation and masking

Eligible patients were randomly assigned (1:1) centrally to defibrotide prophylaxis plus best supportive care (defibrotide prophylaxis group) or best supportive care alone (best supportive care group) using an interactive web response system. The investigator or designee accessed the interactive web response system to obtain treatment assignments for participants eligible for the study. The sponsor remained masked to the master randomisation code until after database lock (Dec 15, 2020). Randomisation was stratified according to the risk of developing sinusoidal obstruction syndrome (high risk or very high risk), age at screening (>16 years or ≤16 years), and country of recruitment. Patients in either treatment group who were diagnosed with sinusoidal obstruction syndrome by the investigator (according to the modified Seattle criteria[16]) were offered defibrotide rescue treatment.

Procedures

Defibrotide (Jazz Pharmaceuticals, Palo Alto, CA, USA) was administered as four equal doses (6·25 mg/kg per dose; 25·00 mg/kg per day total) as 2 h infusions given every 6 h, beginning within 24 h before the start of conditioning and continuing for a recommended duration of 21 days or more (ending no more than 30 days after HSCT). Patients in the best supportive care group received standard-of-care therapy according to institutional guidelines and patient need, beginning on the first day of HSCT conditioning and continuing until 30 days after HSCT, hospital discharge, or a diagnosis of sinusoidal obstruction syndrome (appendix p 1).

For the prophylaxis phase, if sinusoidal obstruction syndrome occurred, the prophylaxis phase ended on the day before the start date of rescue defibrotide; if sinusoidal obstruction syndrome did not occur, the prophylaxis phase ended on the date of study completion or early termination. For patients who developed sinusoidal obstruction syndrome and received rescue defibrotide, the rescue phase began on the start date of rescue defibrotide and ended on the date of study completion or early termination.

Safety assessments included continuous monitoring of treatment-emergent adverse events and serious treatment-emergent adverse events through investigator observation, patient reporting of events, and laboratory findings (at day 30, weekly until day 60, and then at day 100 and day 180 [or at study completion or early termination] after HSCT). All adverse events were classified and reported by investigators using the Common Terminology Criteria for Adverse Events (version 4.03); coding was based on MedDRA (version 19.1).

Safety laboratory tests were assessed at screening and at least once-a-week (coagulation parameters) or three times a week (serum chemistry and haematology assessments) throughout the study, as medically permissible, especially in paediatric patients. Bilirubin concentration was required to be assessed daily during hospitalisation as per each site's standard practice. Follow-up continued up to 6 months (up to day 180) after HSCT. All patients were free to withdraw from participation at any time and for any reason; the investigator could also remove a patient from the study at any time and for any reason.

The Endpoint Adjudication Committee (EPAC), comprised of three independent HSCT specialists who were board certified in haematology or oncology, independently and remotely reviewed the masked electronic patient clinical data and liver ultrasound imaging reports to retrospectively diagnose sinusoidal obstruction syndrome using the modified Seattle criteria.[16] Adjudication was based both on whether a patient met modified Seattle criteria for sinusoidal obstruction syndrome (yes or no) and on the specific criteria met (ie, hyperbilirubinaemia, ascites, hepatomegaly, or weight gain). Disease severity and administration of defibrotide rescue treatment were not determined by EPAC. Two EPAC evaluators assessed each patient's data. If they agreed on both the diagnosis and criteria, the assessment was regarded as complete; if not, a third EPAC evaluator assessed the data. If the third EPAC evaluator agreed on both the diagnosis and the criteria with either of the two other evaluations, the assessment was considered complete; if not, consensus adjudication decisions were made by majority vote (two of three). Investigator-assessed sinusoidal obstruction syndrome was also captured as part of the trial. The decision to treat with rescue defibrotide was made on the basis of investigator assessment of sinusoidal obstruction syndrome. The Independent Data Monitoring Committee (IDMC) was only made aware of the results from the EPAC assessments and was not presented with investigator assessment data, nor were they provided information on any potential discrepancies between EPAC and investigator assessments of sinusoidal obstruction syndrome at the interim analysis.

Outcomes

The primary endpoint was sinusoidal obstruction syndrome-free survival by day 30 after HSCT, based on sinusoidal obstruction syndrome diagnosis as assessed by an independent EPAC. This composite endpoint that considers either sinusoidal obstruction syndrome diagnosis (by EPAC) or death by day 30 as an event was chosen on the basis of guidance from the US Food and Drug Administration. The key secondary endpoint was sinusoidal obstruction syndrome-free survival at day 100 after HSCT (per EPAC assessment).

Other prespecified secondary endpoints were incidence of sinusoidal obstruction syndrome and incidence of acute graft-versus-host disease by day 30, 100, and 180 after HSCT; incidence of sinusoidal obstruction syndrome-associated multiorgan dysfunction by day 30 and 100 after HSCT (in those who developed sinusoidal obstruction syndrome); sinusoidal obstruction syndrome resolution by day 180 after HSCT; non-relapse mortality by day 100 and 180 after HSCT; sinusoidal obstruction syndrome-free survival at 180 days after HSCT; graft failure and time to neutrophil and platelet engraftments; pharmacokinetics; and quality of life assessments. Secondary endpoints of sinusoidal obstruction syndrome free-survival 180 days after HSCT, graft failure, time to neutrophil and platelet engraftment, pharmacokinetics, and quality of life are not reported in this Article.

Prespecified exploratory objectives were immunogenicity assessments, evaluation of predictive or prognostic biomarkers, and health economics and hospital resource utilisation; these analyses are not reported in this Article.

Sinusoidal obstruction syndrome-free survival by day 30 as per investigator diagnosis of sinusoidal obstruction syndrome was part of the concordance analyses between EPAC and investigator diagnosis of sinusoidal obstruction syndrome.

Statistical analysis

A sample size of 400 patients (200 patients per treatment group) was estimated to provide 90% power to detect a hazard ratio (HR) of 0·46 for the primary endpoint in the defibrotide prophylaxis group compared with the best supportive care group, with an average of 68 events in total. The HR of 0·46 was based on an estimated 86% sinusoidal obstruction syndrome-free survival rate at day 30 in the defibrotide prophylaxis group and a 72% sinusoidal obstruction syndrome-free survival rate in the best supportive care group. These assumptions were

based on results from the phase 3 defibrotide prophylaxis study by Corbacioglu and colleagues.[12]

The study had an adaptive design. Due to uncertainties associated with the study design assumptions, specifically the background rate of events in the best supportive care group and the size of the treatment effect, a preplanned interim analysis was to occur when 70% of patients were evaluable for the primary endpoint, with prespecified rules for efficacy stop (one-sided α 0·0005), futility stop (at ≤10% conditional power), and possible sample size re-estimation up to 600 patients.

The interim analysis was done on April 29, 2020 by an Independent Statistical Centre for review by an IDMC, including the first 280 patients randomly assigned. After the targeted assessments of the primary endpoint were observed, the data were cleaned, and a snapshot of the database was transferred to the Independent Statistical Centre to produce the results that were then presented to the IDMC. The IDMC was responsible for reviewing the interim analysis results and making recommendations based on the prespecified rules. The IDMC was also responsible for reviewing the safety data throughout the study at 6-month intervals.

To maintain an overall significance level at a one-sided α of 0·025, the incremental α was specified at one-sided 0·0005 for the interim analysis and one-sided 0·025 for the final analysis. To control the study-wise type one error, sequential testing began with the primary endpoint; if it was significant, the key secondary endpoint test was done at a one-sided α of 0·025. If the primary endpoint was not significant, the results of the key secondary endpoint were considered descriptive and p values were nominal. Results for all other secondary endpoints were descriptive and p values were nominal. SAS (version 9.3 or later) was used for statistical analyses.

The primary endpoint was analysed in the intention-to-treat (ITT) population, including all randomly assigned patients. A stratified log-rank test was done for which the strata were defined by risk status (high risk *vs* very high risk) and age group (paediatric [≤16 years] *vs* adult [>16 years]). For patients with an EPAC assessment of no sinusoidal obstruction syndrome who were still alive at day 30, the censoring date was defined based on the date of last assessments for the modified Seattle criteria components (total bilirubin, weight gain or ascites evaluation, and hepatomegaly evaluation) or the last biopsy assessment, whichever occurred last. Only assessment dates occurring on or before day 30 were taken into consideration when censoring. If the patient was still alive at day 30 and had EPAC-assessed sinusoidal obstruction syndrome after day 30, the censoring date was day 30. Patients assessed for the primary endpoint before the interim analysis were included in the stage one sample and those assessed after the interim analysis were included in the stage two sample. The method set out by Cui and colleagues[17] was used in the final analysis

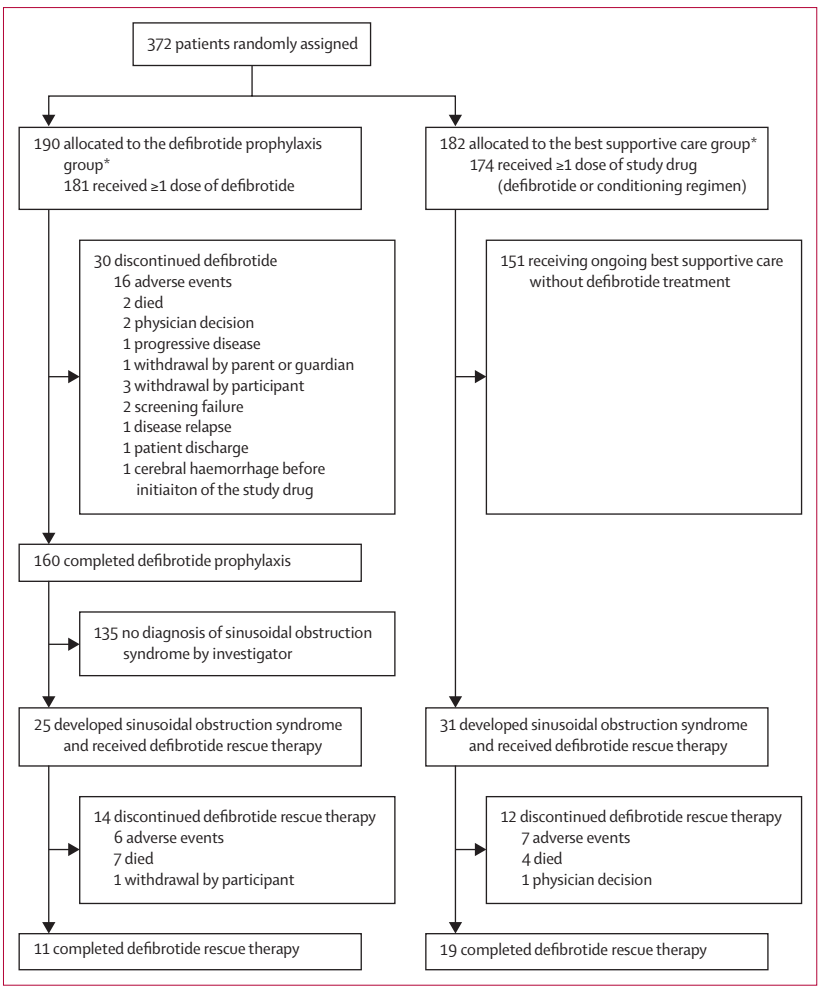

Figure 1: **Study profile**
HSCT=haematopoietic stem-cell transplantation. *Intention-to-treat population used for the primary analysis; 19 patients did not receive HSCT (11 in the defibrotide prophylaxis group and eight in the best supportive care group); two patients in the defibrotide prophylaxis group received one or more doses of defibrotide but did not receive HSCT.

to combine the independent increments of the stratified log-rank statistics from stage one and stage two. Kaplan-Meier estimates of sinusoidal obstruction syndrome-free survival were calculated for the treatment groups. The timing variable was anchored at the date of HSCT (time zero). It was anticipated that less than 2% of patients would not undergo HSCT; for those patients, time zero was the date of randomisation. The timing variable was defined as the number of days from time zero until a diagnosis of sinusoidal obstruction syndrome or death by day 30, whichever came first. The key secondary endpoint, sinusoidal obstruction syndrome-free survival at day 100, was analysed similarly in the ITT population. Safety data were summarised by study phase (prophylaxis or rescue) and by treatment received during the prophylaxis phase (defibrotide *vs* best supportive care).

The concordance analysis was done in the modified ITT population, which included all patients in the ITT

	Defibrotide prophylaxis group (n=190)	Best supportive care group (n=182)
Sex		
Female	90 (47%)	82 (45%)
Male	100 (53%)	100 (55%)
Race		
Asian	39 (21%)	46 (25%)
Black or African American	5 (3%)	8 (4%)
Native Hawaiian or other Pacific Islander	0	2 (1%)
White	125 (66%)	109 (60%)
Multiple	2 (1%)	0
Not reported	19 (10%)	17 (9%)
Ethnicity		
Hispanic or Latino	22 (12%)	21 (12%)
Not Hispanic or Latino	150 (79%)	143 (79%)
Not reported	18 (9%)	17 (9%)
Unknown	0	1 (1%)
Age at screening, years	13 (4–40)	15 (4–44)
Age group		
≤16 years	104 (55%)	94 (52%)
0 to <2 years	17 (9%)	17 (9%)
2 to 11 years	69 (36%)	66 (36%)
12 to 16 years	18 (9%)	11 (6%)
>16 years	86 (45%)	88 (48%)
Risk category		
High risk	108 (57%)	103 (57%)
Very high risk	82 (43%)	79 (43%)
Previous inotuzumab ozogamicin or gemtuzumab ozogamicin exposure	51 (27%)	47 (26%)
Previous tacrolimus exposure	2 (1%)	2 (1%)
Previous sirolimus exposure	0	0
Primary disease in more than 5% of patients		
Acute myeloid leukaemia	52 (27%)	44 (24%)
Acute lymphoblastic leukaemia	49 (26%)	51 (28%)
Neuroblastoma	27 (14%)	30 (16%)
Osteopetrosis	11 (6%)	14 (8%)
(Continued from previous column)		
Time since initial diagnosis, days	251 (155–534)	248 (160–532)
Type of HSCT*		
Allogeneic HSCT	145/179 (81%)	142/174 (82%)
Unrelated donor†	73/145 (50%)	71/142 (50%)
Autologous	32/179 (18%)	32/174 (18%)
Other‡	2/179 (1%)	0
Source of graft*		
Peripheral blood	109/179 (61%)	121/174 (70%)
Bone marrow	52/179 (29%)	39/174 (22%)
Umbilical cord	15/179 (8%)	13/174 (7%)
Other‡	3/179 (2%)	1/174 (1%)
Conditioning regimen*		
Myeloablative conditioning	123/180 (68%)	119/174 (68%)
Reduced-intensity conditioning	10/180 (6%)	7/174 (4%)
Non-myeloablative conditioning	5/180 (3%)	3/174 (2%)
Not specified§	42/180 (23%)	45/174 (26%)

Data are n (%), n/N (%), or median (IQR). Percentages might not total 100%, due to rounding. HSCT=haematopoietic stem-cell transplantation. ITT=intention-to-treat population. *Denominator is the number of patients from the ITT population who reported data on the case report form for the given question. †Denominator is the number of patients who received an allogeneic HSCT. ‡Included patients who had multiple types of graft, sources of graft, or degree of matching records. §Certain diagnoses, such as patients at very high risk of disease who had received previous treatment with an ozogamicin-containing monoclonal antibody, and Class III, high-risk thalassaemia, did not require specified conditioning regimen per study protocol, hence patients with these conditions were eligible regardless of the type of conditioning regimen used.

Table 1: **Baseline demographics and clinical characteristics in the ITT population**

population who had an HSCT. The safety population included all randomly assigned patients who received at least one dose of defibrotide or one dose of conditioning regimen and best supportive care. Subgroup analyses were based on EPAC assessment of sinusoidal obstruction syndrome and included adult and paediatric patient populations and high-risk and very high-risk patient populations.

Post-hoc analyses were sinusoidal obstruction syndrome-free survival at day 30 and day 100 after HSCT, based on investigator-diagnosed sinusoidal obstruction syndrome, for the following risk groups of interest: patients with previous gemtuzumab ozogamicin or inotuzumab ozogamicin exposure, patients with previous or concurrent tacrolimus use, and paediatric patients with a primary diagnosis of osteopetrosis, neuroblastoma, thalassaemia, or haemophagocytic lymphohistiocytosis. p values reported for post-hoc subgroup analyses are one-sided in the ITT population. This study is registered with ClinicalTrials.gov, NCT02851407.

Role of the funding source

Representatives from the sponsor were responsible for the study design, data collection, data analysis, and interpretation of the data.

Results

Between Jan 11, 2017, and Oct 20, 2020, 372 patients were screened for inclusion. At the completion of the planned interim analysis on the first 280 recruited patients, 372 patients (172 [46%] women and 200 [54%] men; median age 14 years [IQR 4·0–40·0]) had been enrolled and randomly assigned to the defibrotide prophylaxis group (190 [51%]) or to the best supportive care group (182 [49%]; figure 1; each participating site recruited 1–17 patients; appendix pp 3–5). At this time, new enrolment in the study was stopped due to futility in the primary endpoint based on the IDMC recommendation.

Enrolment discontinuation was not related to safety concerns; patients already enrolled were allowed to continue and complete the study. The safety population included 181 patients in the defibrotide prophylaxis group and 174 patients in the best supportive care group.

Baseline demographics and clinical characteristics are reported in table 1. The median age at screening was 13·0 years (IQR 4·0–40·0) in the defibrotide prophylaxis group and 15·0 years (4·0–44·0) in the best supportive care group. The most common primary diseases occurring in more than 5% of patients in both groups were acute myeloid leukaemia, acute lymphoblastic leukaemia, and neuroblastoma (table 1). In both groups, a higher proportion of patients received peripheral blood than bone marrow as the graft source (table 1).

In the prophylaxis phase, the mean duration of defibrotide treatment was 28·2 days (SD 8·1) in the defibrotide prophylaxis group and the mean daily defibrotide dose was 22·89 mg/kg per day (SD 4·55). During the rescue phase, the mean duration of treatment was 22·2 days (SD 18·9) in the defibrotide prophylaxis group and 23·2 days (13·3) in the best supportive care group. The mean daily dose was 21·52 mg/kg per day (SD 5·94) in the defibrotide prophylaxis group and 20·43 mg/kg per day (7·23) in the best supportive care group.

In the ITT population, the primary endpoint analysis showed that sinusoidal obstruction syndrome-free survival at day 30 after HSCT (per EPAC assessment) was similar in both treatment groups (log rank statistic –1·04; p=0·85). The Kaplan-Meier estimated sinusoidal obstruction syndrome-free survival at day 30 was 67% (95% CI 58–74) in the defibrotide prophylaxis group and 73% (62–80) in the best supportive care group (HR 1·27 [95% CI 0·84–1·93]; p=0·85; figure 2A). 90 (24%) of 372 patients had an event for the primary endpoint. Most events were sinusoidal obstruction syndrome as assessed by the EPAC (47 [94%] of 50 events in the defibrotide prophylaxis group; 38 [95%] of 40 events in the best supportive care group) and the rest were death without sinusoidal obstruction syndrome (three [6%] events in the defibrotide prophylaxis group; two [5%] events in the best supportive care group).

Analysis of the key secondary endpoint, sinusoidal obstruction syndrome-free survival at day 100 after HSCT (per EPAC assessment), yielded similar results (log rank statistic –0·90; nominal p=0·82), with a Kaplan-Meier estimated sinusoidal obstruction syndrome-free survival at day 100 of 50% (95% CI 26–70) in the defibrotide prophylaxis group and 57% (37–73) in the best supportive care group (HR 1·21 [95% CI 0·84–1·75]; p=0·82; figure 2B). Subgroup analyses by age group and risk status were consistent with the overall results (data not reported).

At day 30, eight (4%) patients in the defibrotide prophylaxis group and eight (4%) patients in the best supportive care group had sinusoidal obstruction syndrome-associated multiorgan dysfunction. At both day 100 and day 180, nine (5%) patients in the defibrotide prophylaxis group and ten (5%) patients in the best supportive care group had sinusoidal obstruction syndrome-associated multiorgan dysfunction.

By day 30, in both treatment groups, the EPAC had retrospectively diagnosed sinusoidal obstruction syndrome more frequently than the investigators who

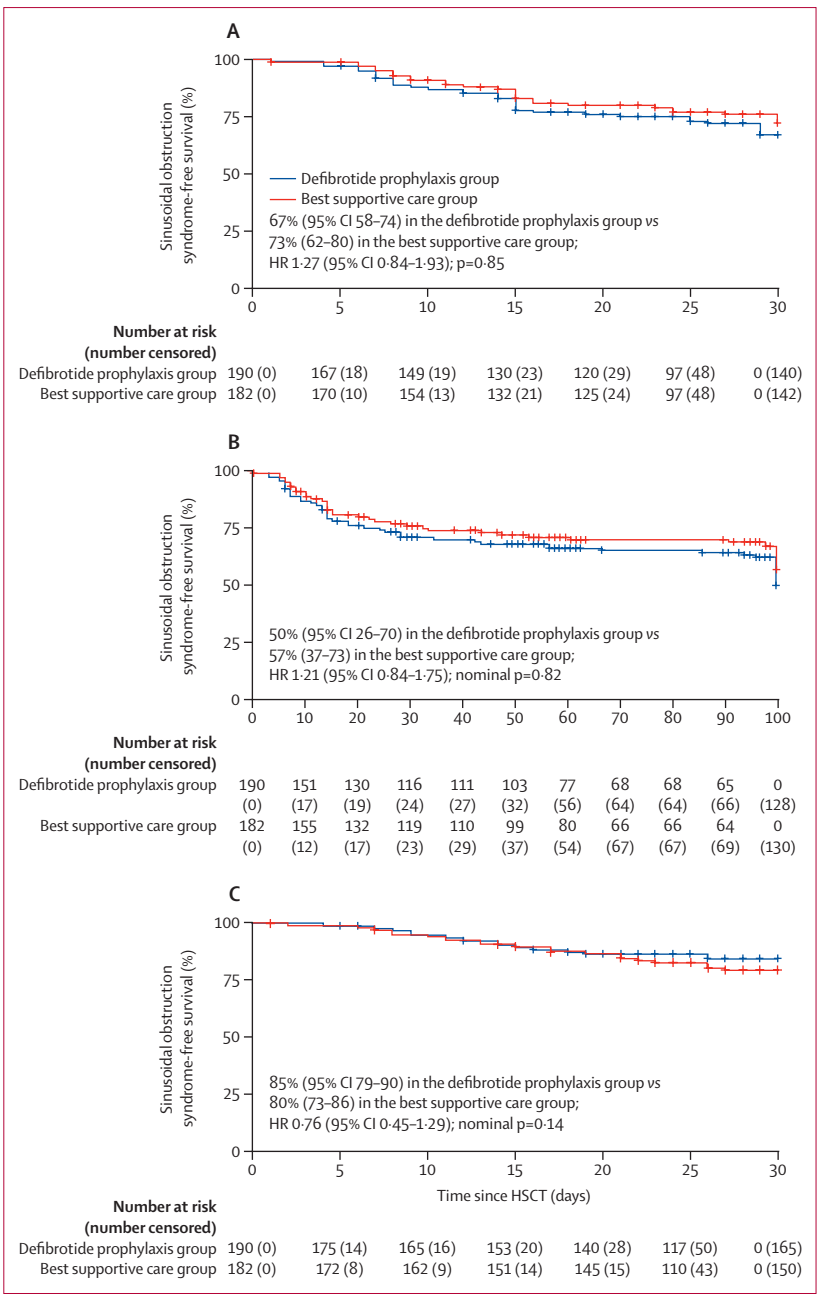

Figure 2: **Sinusoidal obstruction syndrome-free survival in the intention-to-treat population**
Kaplan-Meier estimate according to sinusoidal obstruction syndrome diagnosis per EPAC assessment at day 30 after HSCT (A), per EPAC assessment at day 100 after HSCT (B), and per investigator assessment at day 30 after HSCT (C). EPAC=Endpoint Adjudication Committee. HR=hazard ratio. HSCT=haematopoietic stem-cell transplantation.

	Defibrotide prophylaxis group (n=179)	Best supportive care group (n=174)
Sinusoidal obstruction syndrome diagnosis (investigator *vs* EPAC assessment)		
Concordance		
Yes–yes	18 (10%)	19 (11%)
No–no	115 (64%)	118 (68%)
Discordance		
No–yes	31 (17%)	22 (13%)
Yes–no	4 (2%)	9 (5%)
Yes–not evaluable†	1 (1%)	1 (1%)
No–not evaluable	10 (6%)	5 (3%)
Timing of sinusoidal obstruction syndrome diagnosis (investigator *vs* EPAC assessment)‡		
Diagnosis dates match§	14/18 (78%)	13/19 (68%)
Investigator diagnosis before EPAC	2/18 (11%)	2/19 (11%)
Investigator diagnosis after EPAC	2/18 (11%)	4/19 (21%)
Overall concordance (yes–yes sinusoidal obstruction syndrome diagnosis dates match or no–no)	129 (72%)	131 (75%)

Data are n (%) or n/N (%). Not all percentages total to 100 due to rounding. EPAC=Endpoint Adjudication Committee. HSCT=haematopoietic stem-cell transplantation; ITT=intention-to-treat. *Includes all patients in the ITT population who underwent HSCT. †Adjudicator determined that data provided were insufficient to make a definitive decision on the presence or absence of sinusoidal obstruction syndrome. ‡Number of patients with a yes–yes sinusoidal obstruction syndrome diagnosis by investigator and EPAC was used as the denominator for timing of sinusoidal obstruction syndrome diagnosis percentages. §When there was both an investigator and EPAC diagnosis, diagnosis dates were considered matched if the difference between the diagnosis dates by the investigator and EPAC was 3 days or less.

Table 2: **Concordance between investigator-assessed and EPAC-assessed sinusoidal obstruction syndrome by day 30 after HSCT in the modified ITT population***

assessed their patients in real time (table 2). Overall, the EPAC and investigators were concordant in 260 (74%; there was concordance of diagnosis in 270 patients; however, 10 patients differed in the timing of concordance [>3 days apart]) and discordant in 93 (26%) of the 353 sinusoidal obstruction syndrome assessments. 53 (15%) of 353 patients were assessed as having sinusoidal obstruction syndrome by the EPAC, but not by investigators. In total, 104 patients required one round of independent EPAC review; 67 (64%) patients required adjudication by a third EPAC member (ie, two rounds of review before diagnosis), and 32 (31%) required a consensus meeting (ie, three rounds of review before diagnosis) because none of the three EPAC members agreed on a diagnosis. 27 (40%) of 67 patients who required two rounds of review and 12 (38%) of 32 patients who required three rounds of review were diagnosed with sinusoidal obstruction syndrome by the investigators. 47 (25%) of 190 patients in the defibrotide prophylaxis group and 38 (21%) of 182 patients in the best supportive care group had sinusoidal obstruction syndrome according to EPAC assessment at day 30, whereas 23 (12%) patients in the defibrotide prophylaxis group and 29 (16%) patients in the best supportive care group had sinusoidal obstruction syndrome according to investigator assessment. Incidences of sinusoidal obstruction syndrome at day 30 by age according to investigator assessment were similar to those observed in the overall population (14 [13%] of 104 paediatric patients in the defibrotide prophylaxis group and 15 [16%] of 94 paediatric patients in the best supportive care group; nine [10%] of 86 adult patients in the defibrotide prophylaxis group and 14 [16%] of 88 adult patients in the best supportive care group).

In a preplanned descriptive analysis, Kaplan-Meier estimated sinusoidal obstruction syndrome-free survival at day 30, based on assessment by the investigators, was not statistically significantly different between the defibrotide prophylaxis group (85% [95% CI 79–90]) and the best supportive care group (80% [73–86]; nominal p=0·14; figure 2C). This observation was similar across age groups: 85% (95% CI 76–91) in paediatric patients in the defibrotide prophylaxis group and 80% (69–87) in paediatric patients in the best supportive care group (nominal p=0·36); and 85% (75–92) in adult patients in the defibrotide prophylaxis group and 81% (71–88) in adult patients in the best supportive care group (nominal p=0·62).

In post-hoc analyses, investigator-assessed sinusoidal obstruction syndrome-free survival rates at day 30 and day 100 were similar between treatment groups in patients in the following risk groups of interest: previous gemtuzumab ozogamicin or inotuzumab ozogamicin exposure, patients with previous or concurrent tacrolimus use, and paediatric patients with a primary diagnosis of osteopetrosis, neuroblastoma, thalassaemia, or haemophagocytic lymphohistiocytosis (appendix pp 6–7).

25 (14%) of 181 patients in the defibrotide prophylaxis group and 31 (18%) of 174 patients in the best supportive care group had sinusoidal obstruction syndrome (as diagnosed by the investigator) at any time after HSCT and received defibrotide as rescue treatment. Sinusoidal obstruction syndrome resolution occurred in 28 (50%) of these 56 patients. Defibrotide rescue treatment was not administered to patients who were diagnosed by EPAC only, so sinusoidal obstruction syndrome resolution was not reported for these patients. 147 (81%) of 181 patients in the defibrotide prophylaxis group and 142 (82%) of 174 patients in the best supportive care had group allogeneic donors. Among these patients, 13 (9%) at day 30, 20 (14%) at day 100, and 22 (15%) at day 180 had acute (grade 2–4) graft-versus-host disease in the defibrotide prophylaxis group, compared with 13 (9%) patients at day 30, 24 (17%) at day 100, and 26 (18%) at day 180 in the best supportive care group.

During the prophylaxis phase, 21 (12%) of 181 patients in the defibrotide prophylaxis group and 17 (10%) of 174 patients in the best supportive care group died; of whom, 15 (40%) died due to primary disease relapse (eight patients in the defibrotide prophylaxis group and seven in the best supportive care group). Across both the prophylaxis and rescue phases, non-relapse mortality was similar between treatment groups: 25 (14%) of 181 patients in the defibrotide prophylaxis group and 23 (13%) of 174 patients in the best supportive care group died.

	Defibrotide prophylaxis group					Best supportive care group				
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Prophylaxis phase										
One or more treatment-emergent adverse events	2/181 (1%)	22/181 (12%)	73/181 (40%)	71/181 (39%)	12/181 (7%)	2/174 (1%)	20/174 (11%)	73/174 (42%)	69/174 (40%)	10/174 (6%)
Most common (≥20%) adverse events, all grades										
Nausea	48/181 (27%)	34/181 (19%)	27/181 (15%)	0	0	42/174 (24%)	42/174 (24%)	14/174 (8%)	0	0
Diarrhoea	55/181 (30%)	38/181 (21%)	12/181 (7%)	1/181 (1%)	0	51/174 (29%)	41/174 (24%)	13/174 (7%)	2/174 (1%)	0
Stomatitis	19/181 (10%)	32/181 (18%)	52/181 (29%)	2/181 (1%)	0	14/174 (8%)	44/174 (25%)	56/174 (32%)	2/174 (1%)	0
Vomiting	59/181 (33%)	35/181 (19%)	9/181 (5%)	0	0	51/174 (29%)	33/174 (19%)	7/174 (4%)	0	0
Abdominal pain	24/181 (13%)	26/181 (14%)	6/181 (3%)	0	1/181 (1%)	17/174 (10%)	24/174 (14%)	4/174 (2%)	0	0
Constipation	22/181 (12%)	11/181 (6%)	1/181 (1%)	0	0	23/174 (13%)	14/174 (8%)	0	0	0
Pyrexia	48/181 (27%)	54/181 (30%)	9/181 (5%)	0	0	59/174 (34%)	39/174 (22%)	11/174 (6%)	2/174 (1%)	0
Hypokalaemia	23/181 (13%)	25/181 (14%)	19/181 (10%)	4/181 (2%)	0	16/174 (9%)	20/174 (11%)	19/174 (11%)	3/174 (2%)	0
Hypomagnesaemia	51/181 (28%)	18/181 (10%)	1/181 (1%)	1/181 (1%)	0	33/174 (19%)	24/174 (14%)	1/174 (1%)	0	0
Decreased appetite	12/181 (7%)	15/181 (8%)	25/181 (14%)	0	0	10/174 (6%)	16/174 (9%)	21/174 (12%)	1/174 (1%)	0
Epistaxis	21/181 (12%)	13/181 (7%)	5/181 (3%)	0	0	30/174 (17%)	11/174 (6%)	4/174 (2%)	0	0
Febrile neutropenia	0	1/181 (1%)	51/181 (28%)	0	0	3/174 (2%)	4/174 (2%)	52/174 (30%)	3/174 (2%)	0
Anaemia	0	6/181 (3%)	39/181 (22%)	4/181 (2%)	0	2/174 (1%)	11/174 (6%)	38/174 (22%)	1/174 (1%)	0
Platelet count decreased	0	1/181 (1%)	3/181 (2%)	29/181 (16%)	0	2/174 (1%)	0	8/174 (5%)	33/174 (19%)	0
Hypertension	11/181 (6%)	40/181 (22%)	17/181 (9%)	0	0	14/174 (8%)	27/174 (16%)	11/174 (6%)	0	0
Acute graft-versus-host disease in skin	15/181 (8%)	12/181 (7%)	5/181 (3%)	0	0	8/174 (5%)	27/174 (16%)	1/174 (1%)	0	0
Headache	20/181 (11%)	28/181 (15%)	1/181 (1%)	0	0	18/174 (10%)	17/174 (10%)	0	0	0
Rescue phase*†										
One or more treatment-emergent adverse events	0	5/25 (20%)	5/25 (20%)	3/25 (12%)	12/25 (48%)	2/31 (6%)	1/31 (3%)	8/31 (26%)	10/31 (32%)	10/31 (32%)
Most common (≥20%) adverse events, all grades										
Constipation	6/25 (24%)	1/25 (4%)	0	0	0	1/31 (3%)	1/31 (3%)	0	0	0
Diarrhoea	3/25 (12%)	4/25 (16%)	0	0	0	2/31 (6%)	3/31 (10%)	1/31 (3%)	1/31 (3%)	0
Abdominal distension	2/25 (8%)	3/25 (12%)	0	0	0	2/31 (6%)	0	0	0	0
Vomiting	2/25 (8%)	2/25 (8%)	1/25 (4%)	0	0	4/31 (13%)	0	0	0	0
Veno-occlusive disease	0	5/25 (20%)	5/25 (20%)	0	4/25 (16%)	2/31 (6%)	1/31 (3%)	8/31 (26%)	5/31 (16%)	2/31 (6%)
Hypertension	1/25 (4%)	3/25 (12%)	2/25 (8%)	0	0	1/31 (3%)	3/31 (10%)	2/31 (6%)	0	0
Hypotension	1/25 (4%)	1/25 (4%)	0	1/25 (4%)	0	3/31 (10%)	1/31 (3%)	2/31 (6%)	3/31 (10%)	0
Pyrexia	3/25 (12%)	2/25 (8%)	1/25 (4%)	0	0	6/31 (19%)	4/31 (13%)	1/31 (3%)	0	0
Blood bilirubin increased	1/25 (4%)	0	3/25 (12%)	2/25 (8%)	0	0	2/31 (6%)	0	0	0
Plate count decreased	1/25 (4%)	0	1/25 (4%)	3/25 (12%)	0	0	1/31 (3%)	1/31 (3%)	0	0
Acute kidney injury	0	1/25 (4%)	0	1/25 (4%)	1/25 (4%)	2/31 (6%)	4/31 (13%)	2/31 (6%)	1/31 (3%)	0
Pleural effusion	2/25 (8%)	1/25 (4%)	1/25 (4%)	1/25 (4%)	0	2/31 (6%)	1/31 (3%)	2/31 (6%)	0	0
Hypokalaemia	3/25 (12%)	1/25 (4%)	2/25 (8%)	0	0	3/31 (10%)	2/31 (6%)	0	1/31 (3%)	0
Anaemia	0	1/25 (4%)	4/25 (16%)	0	0	0	0	3/31 (10%)	0	0
Veno-occlusive liver disease	1/25 (4%)	0	4/25 (16%)	0	0	0	0	0	3/31 (10%)	0

Data are n/N (%). Incidence was based on the number of patients from the safety analysis set per phase, not the number of events; patients could have had more than one event for a given term per phase. In the prophylaxis phase, all patients who received treatment were included (181 in the defibrotide group and 174 in the best standard of care group). *In the rescue phase, the denominator is the number of patients who entered the rescue phase in each arm (25 in the defibrotide group and 31 in the best standard of care group). †All patients in both groups received defibrotide in the rescue phase.

Table 3: **Most common individual treatment-emergent adverse events in the safety population**

Treatment-related treatment-emergent adverse events were as expected (appendix pp 8–9); no new defibrotide-related safety signals were identified. Treatment-emergent adverse events were similar between groups during the prophylaxis phase, and tended to be related to the transplantation rather than study drug (table 3). In the prophylaxis phase, almost all patients had at least one treatment-emergent adverse event. Of note, the number of bleeding events (pulmonary haemorrhage) was similar between the two groups. The most common grade 3 or 4 treatment-emergent adverse events were stomatitis (grade 3, 52 [29%] of 181 patients in the defibrotide prophylaxis group and 56 [32%] of 174 patients in the best supportive care group; grade 4, two [1%] in the defibrotide prophylaxis group and two [1%] in the best supportive care group) and febrile neutropaenia (grade 3, 51 [28%] in the defibrotide prophylaxis group and 52 [30%] in the best supportive care group; grade 4, no patients in the defibrotide prophylaxis group and three [2%] in the best supportive care group). Treatment-emergent adverse events of special interest are summarised in the appendix (pp 8–9). Serious treatment-emergent adverse events occurred in 74 (41%) of 181 patients in the defibrotide prophylaxis group and 61 (35%) of 174 patients in the best supportive care group. Sixteen (9%) patients in the defibrotide prophylaxis group had treatment-related treatment-emergent adverse events leading to study drug discontinuation (appendix pp 8–9). Ten (6%) patients in the defibrotide prophylaxis group and ten (6%) patients in the best supportive care group had treatment-emergent adverse events leading to death (appendix pp 10–11).

In the rescue phase, when patients developing sinusoidal obstruction syndrome in both treatment groups received defibrotide as rescue treatment, all of the patients in both groups had at least one treatment-emergent adverse event (appendix pp 8–9). Two (8%) of 25 patients in the defibrotide prophylaxis group and three (10%) of 31 patients in the best supportive care group who received rescue therapy had treatment-related adverse events leading to study drug discontinuation (appendix pp 8–9). Twelve (48%) patients in the defibrotide prophylaxis group and eight (26%) patients in the best supportive care group had treatment-emergent adverse events leading to death (appendix pp 10–11). One (4%) patient in the defibrotide prophylaxis group (intracranial haemorrhage) and one (3%) patient in the best supportive care group (sinusoidal obstruction syndrome) had treatment-related treatment-emergent adverse events leading to death.

Grade 1 and 2 treatment-emergent adverse events occurring in at least 10% of patients in the defibrotide prophylaxis group are shown in the appendix (pp 13–15). All grade 3 to grade 5 treatment-emergent adverse events for both the defibrotide prophylaxis and the best supportive care groups are shown in the appendix (pp 16–48).

Mortality rates were 18% (28 of 190) in the defibrotide prophylaxis group and 13% (20 of 182) in the best supportive care group at day 100, and 32% (35 of 190) in the defibrotide prophylaxis group and 29% (30 of 182) in the best supportive care group at day 180. Causes of death tended to be disease relapse or were transplantation-related, and were generally not related to defibrotide treatment.

Discussion

Sinusoidal obstruction syndrome of the liver is a potentially life-threatening complication of HSCT that requires strict vigilance and patient monitoring to effectively diagnose and treat. This phase 3, open-label, randomised study compared the efficacy and safety of adding defibrotide to best supportive care with best supportive care alone for the prevention of sinusoidal obstruction syndrome in patients undergoing HSCT who were at high risk or very high risk of developing sinusoidal obstruction syndrome. On the basis of recommendations from the IDMC following review of a preplanned interim analysis, enrolment was prematurely stopped for presumed futility; study termination was not due to any safety findings. The interim analysis used EPAC adjudication of sinusoidal obstruction syndrome and showed that the study was unlikely to reach statistical significance in the final analysis of the primary endpoint if the study were to complete enrolment.

Sinusoidal obstruction syndrome was diagnosed more frequently by the EPAC than by the investigators in both treatment groups. Differences between EPAC and investigator assessments of sinusoidal obstruction syndrome highlight challenges in the diagnosis of the disease. EPAC-assessed incidence of sinusoidal obstruction syndrome was higher than expected based on existing literature, which typically reports incidences from 5% to 12% following defibrotide prophylaxis and 16% to 20% in controls,[12,13] suggesting potential over-diagnosis of sinusoidal obstruction syndrome; incidence of sinusoidal obstruction syndrome by investigator assessment was more in line with the literature. EPAC members were removed from the bedside, with remote diagnoses made based on snapshots of clinical information. Moreover, the EPAC followed a diagnostic algorithm and did not have the opportunity to assess data in conjunction with close monitoring of the patient; thus, because EPAC judgement of sinusoidal obstruction syndrome was based on a checklist of parameters, patients could have been diagnosed based on a transient, non-sustained alteration of a key parameter. By contrast, the investigators were able to closely monitor the patient on a daily basis as part of their care team and had the clear advantage of continuity. Although there might have been a bias from investigators toward sinusoidal obstruction syndrome diagnosis in the best supportive care group compared with the defibrotide prophylaxis group, given that investigators were not masked to the

study treatment, the rate of sinusoidal obstruction syndrome diagnosis in the best supportive care group was still lower by investigator assessment versus EPAC. Additionally, the incidence of sinusoidal obstruction syndrome at day 30 based on EPAC assessment (25% in the defibrotide prophylaxis group *vs* 21% in the best supportive care group) was not only higher than sinusoidal obstruction syndrome diagnosis by investigator assessment (defibrotide prophylaxis group 12% *vs* best supportive care group 16%), but was also substantially higher than the previously reported incidence in the prevention setting and the current incidence of sinusoidal obstruction syndrome without prevention.[12,13]

In this study, rates of investigator-assessed sinusoidal obstruction syndrome were similar between treatment groups and by patient age. A 2021 systematic review of defibrotide prophylaxis for sinusoidal obstruction syndrome showed that the overall incidence of sinusoidal obstruction syndrome was also similar between adults (5% [95% CI 3–8]) and paediatric patients (8% [6–10]).[13] Previous retrospective, single-centre prevention studies showed that adults receiving defibrotide prophylaxis generally had better survival outcomes than those in the control group,[18,19] although direct comparisons between studies cannot be made. In a phase 3 study of defibrotide prophylaxis in paediatric patients at a high risk of sinusoidal obstruction syndrome, disease incidence at day 30 after HSCT was lower with defibrotide prophylaxis (12%) versus controls (20%; risk difference –7·7% [95% CI –15·3 to –0·1]; p=0·05).[12] Although sinusoidal obstruction syndrome-related mortality at day 100 after HSCT was similar in the defibrotide prophylaxis group (2%) and the control group (6%), mortality rates on day 100 after HSCT were higher in patients with sinusoidal obstruction syndrome (25%) than in those without the disease (6%; risk difference 18·6% [95% CI 7·1 to 30·1]).[12] In another study of paediatric patients, 9% of patients in the defibrotide prophylaxis group and 7% of patients in the control group developed sinusoidal obstruction syndrome after HSCT, but all patients in the defibrotide prophylaxis group were alive at the time of the analysis, compared with 50% in the control group.[20]

Safety results in our study were consistent with the known safety profile of defibrotide, and no new safety signals were identified.[12,21] A similar proportion of patients in both groups had treatment-emergent adverse events, serious treatment-emergent adverse events, and treatment-emergent adverse events of special interest, supporting the safety of defibrotide in this setting. There did not appear to be an increased bleeding risk with the use of defibrotide for sinusoidal obstruction syndrome prophylaxis: the rates of haemorrhage were similar between the defibrotide prophylaxis and best supportive care groups. The absence of an increased risk of bleeding supports previous findings on the incidence of bleeding with defibrotide versus control: cumulative incidence of haemorrhage was 22% in the defibrotide group versus 21% in the control group, and was 1% in the defibrotide group versus 8% in the control group when studied outside of the post-HSCT sinusoidal obstruction syndrome setting.[12,22]

This study has some limitations. The eligibility criteria specified enrolling patients at high and very high risk for sinusoidal obstruction syndrome. The risk groups in the study protocol might not accurately reflect the current clinical opinion regarding these patients. Due to the constantly changing landscape of therapies and patient care, what was considered high risk at the study start might no longer be relevant. Specifically, there was poor representation of key at-risk groups, such as patients who have previously received sirolimus, in whom sinusoidal obstruction syndrome has been recognised to be significantly more common and in whom defibrotide appears to be especially active.[23,24] Additionally, findings from the post-hoc analyses of investigator-assessed sinusoidal obstruction syndrome-free survival in key risk groups of interest are limited by insufficient statistical power. Furthermore, because sinusoidal obstruction syndrome severity was not assessed, the ability to generalise these trial results is restricted. This trial was an international, multicentre, phase 3 study, and it is possible that the heterogeneity of patient characteristics, the challenging nature of the selected study endpoints, and discrepancies identified during the independent adjudication led to a different outcome compared with other trials in this setting.

To the best of our knowledge, the use of a composite endpoint was unique to this study. Given the disease complexity and the requirement for a crossover to treatment, interpretation of the effects of defibrotide on outcomes following a diagnosis of sinusoidal obstruction syndrome is difficult. Additionally, both liver imaging and sinusoidal obstruction syndrome diagnosis were centrally adjudicated, whereas most trials in this setting have only one element of central adjudication (eg, imaging). Moreover, although prespecified censoring rules were in place for the primary endpoint to handle patients who started rescue treatment but did not have EPAC-confirmed sinusoidal obstruction syndrome, the diagnosis of sinusoidal obstruction syndrome by EPAC did not influence the decision of investigators to treat sinusoidal obstruction syndrome with defibrotide. Furthermore, this might complicate interpretation of the results based on EPAC assessment outside of the primary endpoint.

In conclusion, in the context of this study and how it was designed, defibrotide did not show a benefit in the prophylaxis of sinusoidal obstruction syndrome. Although the study was unsuccessful—with decisions regarding the final trial design made after incorporating input and direction from registry data, regulatory authorities, the study sponsor, and the steering committee—the composite of sinusoidal obstruction syndrome-free survival has not been used as an endpoint

in previous nor subsequent studies of defibrotide. Previous studies have shown a benefit with defibrotide prophylaxis, reducing the overall incidence of sinusoidal obstruction syndrome. Given the high mortality rate associated with sinusoidal obstruction syndrome, more studies on strategies to prevent development of the disease with a focus on high-risk groups in current HSCT practise are warranted.

Contributors

SAG, SC, AP, and PGR participated in the study steering committee. HJK, TT, SLK, and PS did the research. SAG, SC, FL, JM, PGR, MM, HJK, SLK, MS, PS, AP, VA, and PL acquired, analysed, or interpreted the data. SAG, SC, FL, AP, and PGR wrote the manuscript. All authors had access to the data and vouch for the analyses and interpretations of the data. VA and PL had access to the raw data and verified the data. All authors critically revised the manuscript and approved the manuscript for submission and take responsibility for publication.

Declaration of interests

SAG reports serving on steering committees or scientific advisory boards for Jazz Pharmaceuticals, Novartis, Adaptimmune, TCR2, Cellectis, Juno, Vertex, Allogene, CBMG, GlaxoSmithKline, J&J/Janssen, and Cabaletta; payment for expert testimony for Jones Day; toxicity management patents managed by Children's Hospital of Philadelphia and University of Pennsylvania policies; serving as a consultant to Gentium/Jazz Pharmaceuticals, Novartis, Roche, GlaxoSmithKline, CBMG, Eureka, and Janssen/J&J; and research funding from Jazz Pharmaceuticals, Novartis, Kite, Vertex, and Servier. TT reports research funding from Chugai, Kyowa Kirin, Fuji Pharma, NIPPON SHINYAKU, Asahi Kasei Pharma, Eisai, Sumitomo Pharma, ONO, Astellas, SHIONOGI, Priothera SAS, LUCA Science, and Otsuka; honoraria from AbbVie, Astellas, NIPPON SHINYAKU, Kyowa Kirin, Novartis, Bristol-Myers Squibb, Sumitomo Pharma, Merck Sharp & Dohme, Celgene, Chugai, and Janssen; and serving on steering committees or scientific advisory boards for Novartis, Meiji Seika Pharma, Daiichi Sankyo, Asahi Kasei Pharma, Astellas, AstraZeneca, Takeda, Janssen, Roche Diagnostics, Sumitom Pharma, Celgene, and Sanofi. PL and VA are employees of and hold stock ownership and/or stock options in Jazz Pharmaceuticals. AP reports payment for lectures and speaker bureaus from Jazz Pharmaceuticals, and has received grant support for travelling and attending the 2022 American Society of Hematology meeting. PGR reports consulting fees from Oncopeptides, Celgene/Bristol-Myers Squibb, Karyopharm, Sanofi, Secura Bio, GlaxoSmithKline, AstraZeneca, Takeda, and Janssen, and research grants from Oncopeptides, Celgene/Bristol-Myers Squibb, Karyopharm, and Takeda. MM reports lectures honoraria from Jazz Pharmaceuticals and honoraria for attending and contributing to advisory boards of Jazz Pharmaceuticals. All other authors declare no competing interests.

Data sharing

All relevant data are provided within the Article and the appendix. Jazz Pharmaceuticals has established a process to review requests from qualified external researchers for data from Jazz Pharmaceuticals sponsored clinical trials in a responsible manner that includes protecting patient privacy, assurance of data security and integrity, and furthering scientific and medical innovation. Additional details on Jazz Pharmaceuticals data sharing criteria and process for requesting access can be found online. Individual patient data will not be shared.

For more on **data sharing criteria and process** see https://www.jazzpharma.com/science/clinical-trial-data-sharing/

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References

1 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:** 157–68.

2 Corbacioglu S, Jabbour EJ, Mohty M. Risk factors for development of and progression of hepatic veno-occlusive disease/sinusoidal obstruction syndrome. *Biol Blood Marrow Transplant* 2019; **25:** 1271–80.

3 Khimani F, McDonald GB, Shulman HM, et al. Hepatic veno-occlusive disease following sirolimus-based immune suppression. *Bone Marrow Transplant* 2019; **54:** 85–89.

4 Faraci M, Bertaina A, Luksch R, et al. Sinusoidal obstruction syndrome/veno-occlusive disease after autologous or allogeneic hematopoietic stem cell transplantation in children: a retrospective study of the Italian Hematology-Oncology Association-Hematopoietic Stem Cell Transplantation Group. *Biol Blood Marrow Transplant* 2019; **25:** 313–20.

5 Bonifazi F, Barbato F, Ravaioli F, et al. Diagnosis and treatment of VOD/SOS after allogeneic hematopoietic stem cell transplantation. *Front Immunol* 2020; **11:** 489.

6 Richardson PG, Carreras E, Iacobelli M, Nejadnik B. The use of defibrotide in blood and marrow transplantation. *Blood Adv* 2018; **2:** 1495–509.

7 Richardson PG, Corbacioglu S, Ho VT, et al. Drug safety evaluation of defibrotide. *Expert Opin Drug Saf* 2013; **12:** 123–36.

8 Hildebrandt GC, Chao N. Endothelial cell function and endothelial-related disorders following haematopoietic cell transplantation. *Br J Haematol* 2020; **190:** 508–19.

9 US Food and Drug Administration. Defitelio. 2016. https://www.accessdata.fda.gov/spl/data/0173efe0-e4e2-41f6-b044-81f707120906/0173efe0-e4e2-41f6-b044-81f707120906.xml (accessed April 2, 2019).

10 European Medical Agency. Defitelio: summary of product characteristics. Accessed 2019. https://www.ema.europa.eu/en/documents/product-information/defitelio-epar-product-information_en.pdf (accessed April 2, 2019).

11 Richardson PG, Palomo M, Kernan NA, Hildebrandt GC, Chao N, Carreras E. The importance of endothelial protection: the emerging role of defibrotide in reversing endothelial injury and its sequelae. *Bone Marrow Transplant* 2021; **56:** 2889–96.

12 Corbacioglu S, Cesaro S, Faraci M, et al. Defibrotide for prophylaxis of hepatic veno-occlusive disease in paediatric haemopoietic stem-cell transplantation: an open-label, phase 3, randomised controlled trial. *Lancet* 2012; **379:** 1301–09.

13 Corbacioglu S, Topaloglu O, Aggarwal S. A systematic review and meta-analysis of studies of defibrotide prophylaxis for veno occlusive disease/sinusoidal obstruction syndrome. *Clin Drug Investig* 2022; **42:** 465–76.

14 Chalandon Y, Simonetta F, Dantin C, et al. Efficient prophylaxis with defibrotide for sinusoidal obstruction syndrome (SOS) after allogeneic hematopoietic stem cell transplantation (HSCT). *Blood* 2016; **128** (suppl 1)**:** 2204 (abstr).

15 Mohty M, Malard F, Abecassis M, et al. Sinusoidal obstruction syndrome/veno-occlusive disease: current situation and perspectives-a position statement from the European Society for Blood and Marrow Transplantation (EBMT). *Bone Marrow Transplant* 2015; **50:** 781–89.

16 McDonald GB, Hinds MS, Fisher LD, et al. Veno-occlusive disease of the liver and multiorgan failure after bone marrow transplantation: a cohort study of 355 patients. *Ann Intern Med* 1993; **118:** 255–67.

17 Cui L, Hung HM, Wang SJ. Modification of sample size in group sequential clinical trials. *Biometrics* 1999; **55:** 853–57.

18 Hasenkamp J, Conradi I, Wulf G, Jung W, Truemper L, Glass B. Prevention of veno-occlusive disease in hematopoietic stem cell transplantation due to defibrotide prophylaxis. *Blood* 2004; **104:** 1139.

19 Tekgunduz E, Akpinar S, Bozdag SC, et al. Effectiveness of defibrotide in the prevention of VOD among patients receiving allogeneic hematopoetic cell transplantation: a retrospective single center experience. *Blood* 2012; **120** (suppl 1)**:** 4508 (abstr).

20 Qureshi A, Marshall L, Lancaster D. Defibrotide in the prevention and treatment of veno-occlusive disease in autologous and allogeneic stem cell transplantation in children. *Pediatr Blood Cancer* 2008; **50:** 831–32.

21 Richardson PG, Soiffer RJ, Antin JH, et al. Defibrotide for the treatment of severe hepatic veno-occlusive disease and multiorgan failure after stem cell transplantation: a multicenter, randomized, dose-finding trial. *Biol Blood Marrow Transplant* 2010; **16:** 1005–17.

22 Tappe W, Aggarwal S, Topaloglu O, Iacobelli M. A meta-analysis evaluating the incidence of bleeding events with intravenous defibrotide treatment outside the veno-occlusive disease/sinusoidal obstruction syndrome setting. *Clin Appl Thromb Hemost* 2020; **26:** 1076029620935202.

23 Nauffal M, Kim HT, Richardson PG, et al. Defibrotide: real-world management of veno-occlusive disease/sinusoidal obstructive syndrome after stem cell transplant. *Blood Adv* 2022; **6:** 181–88.

24 Strouse C, Zhang Y, Zhang MJ, et al. Risk score for the development of veno-occlusive disease after allogeneic hematopoietic cell transplant. *Biol Blood Marrow Transplant* 2018; **24:** 2072–80.