PASS INFORMATION

Title	A multi-centre, multinational, prospective observational registry to collect safety and outcome data in patients diagnosed with severe hepatic veno-occlusive disease (VOD) following haematopoietic stem cell transplantation (HSCT) and treated with Defitelio®
Protocol version identifier	DF VOD-2013-03-REG, Version 2
Date protocol	28 November 2018
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Active substance	Defibrotide (ATC code B01AX01)
Medicinal product	Defitelio
Product reference	EU/1/13/878
Procedure number	EMEA/H/C/002393
Marketing authorisation holder	Gentium S.r.L PiazzaXX Settembre 2 Villa Guardia 22079 Italy
Joint PASS	No
Research question and objectives	Assess the incidence rate of specific serious adverse events of interest (including fatalities) and evaluate outcome in patients with severe hepatic VOD post-HSCT, treated with Defitelio
Countries of study	France Portugal Italy UK
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1. LIST OF ABBREVIATIONS

AE	Adverse Event
ALL	Acute Lymphoblastic Leukemia
AML	Acute Myelogenous Leukemia
ATG	Anti-thymocyte globulin
CI	Confidence Interval
CHMP	Committee for Medicinal Products for Human Use
e-Form	registry-specific electronic case reporting form
CML	Chronic myelogenous (or myeloid) leukemia
CRA	Clinical research associate
CRF	Case report form
CSR	Clinical Study Report
EBMT	European Society for Blood and Marrow Transplantation
EDC	Electronic Data Capture
EEA	European economic area
EMEA	European Medicine Agency
FMAS	Familial Macrophage activating syndrome
GvHD	Graft-versus-host disease
ICH	International Conference on Harmonization
IND	Investigational New Drug
HSCT	Haematopoietic Stem Cell Transplantation
MedDRA	Medical Dictionary for Regulatory Activities
MOF	Multi-organ Failure
NDA	New Drug Application
OP	Osteopetrosis
PAI-1	Plasminogen activator inhibitor-1
PT	Preferred Term
ProMISe	Project Manager internet server
RUQ	Right Upper Quarter
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SD	Standard Deviation
SOB	Specific Obligation
SOC	System Organ Class
SPC	Summary of product characteristics
t-PA	tissue plasminogen activator
VOD	Veno-occlusive Disease
WHO	World Health Organization
WMA	World Medical Association

2. RESPONSIBLE PARTIES

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3. ABSTRACT

Title of the Study

A multi-centre, multinational, prospective observational registry to collect safety and outcome data in patients diagnosed with severe hepatic veno-occlusive disease (VOD) following haematopoietic stem cell transplantation (HSCT) and treated with Defitelio®.

Protocol code: DF VOD-2013-03-REG, Version 2, 28 November 2018.

Rationale and Background

Defitelio is indicated for the treatment of severe hepatic VOD also known as sinusoidal obstruction syndrome in HSCT therapy in adults and in adolescents, children and infants over 1 month of age.

Defitelio has been granted a Marketing Authorisation in Europe on 18 October 2013 under exceptional circumstances.

As a specific obligation, Gentium has been required to set up a disease registry to collect safety and outcome data, and to assess patterns of utilisation of Defitelio in the post-approval setting.

This is a multi-centre, multinational and prospective observational (non-interventional) disease registry of patients with severe hepatic VOD following HSCT and treated with Defitelio.

Gentium has been required to ensure that information regarding all potential and identified risks reported in the most recent version of the Risk Management Plan is being collected.

On 23 January 2014, Jazz became the indirect majority shareholder of Gentium. Whilst Gentium remains the marketing authorisation holder ("MAH") of Defitelio in Europe, Jazz performs several activities on behalf of Gentium, including but not limited to clinical, medical information, pharmacovigilance and regulatory, which includes this post-authorisation safety study DF VOD-2013-03 REG:T.

Hepatic VOD is one of the most common life-threatening regimen-related toxicities that constitute a barrier to successful allogeneic and autologous HSCT. VOD is characterised by rapid weight gain, painful hepatomegaly, hyperbilirubinemia/jaundice, and ascites/fluid retention, without other identifiable causes for liver disease (Richardson, 2012). In a recent survey on 135 studies performed between 1997 and October 2007, the overall mean incidence of VOD in patients undergoing HSCT has been reported to be 13.7% with a lower rate of 9.6% when Baltimore criteria were applied (Coppell, 2010).

The severe form of the disease, usually associated with pulmonary dysfunction or renal dysfunction (i.e., multi-organ failure, MOF), with or without encephalopathy, and a mortality rate of more than 80% by 100 days after HSCT, is reported to occur in about 40%-60% of VOD patients, that is approximately 3-5% of transplanted patients.

Given the low incidence of severe hepatic VOD and the varying size of bone marrow transplant centres in EU, in order to collect meaningful clinical data, the registry will be conducted in

European transplant centres that are members of the European Society for Blood and Marrow Transplantation (EBMT), where possible.

Research Question and Objectives

The main objective of the registry is to assess the incidence rate of specific serious adverse events (SAEs) of interest (including fatalities) in patients with severe hepatic VOD post-HSCT treated with Defitelio.

Study Design

Multi-centre, multinational, prospective observational study based on the EBMT registry system.

Population

Patients undergoing HSCT and diagnosed with severe hepatic VOD, who agree to participate in the study.

Variables

- Incidence rate of specific SAEs of interest
- Incidence rate of MOF and graft-versus-host disease (GvHD) in adult and paediatric patients
- Survival by Day+100 post-HSCT, overall survival and mortality due to VOD
- Rate of VOD and VOD with MOF resolution any time after treatment initiation
- Characteristics of patients with severe hepatic VOD treated with Defitelio (age, gender, patients with pre-existing liver or severe renal insufficiency; patient with intrinsic lung disease, etc.)
- Other uses of Defitelio (indications) in the transplant setting

Data Sources

Data will be collected from physicians contributing to the EBMT registry on their patients, as routinely monitored during clinical practice. Data will be entered by the treating physician or delegate in a registry-specific case reporting form separate from the other EBMT information (APPENDIX 1).

Study Size

Study size is based on the number of available patients (who were treated with Defitelio) listed in the database (participating sites were notified to cease patient recruitment as of 18 July 2018) (n=163) after receiving positive opinion from the Committee for Medicinal Products for Human Use (CHMP) on 28 June 2018.

Data Analysis

The study population is defined as the population of subjects with severe hepatic VOD post-HSCT who are entered into the registry. This population is the primary population for the evaluation of both the safety of Defitelio and outcome.

Baseline data will be summarised. For continuous variables such as age, summary statistics will include number of patients (n), mean, median, standard deviation and range (minimum – maximum). For binary and categorical data, such as gender and primary diagnosis, summary statistics will include n and frequency (absolute and percentage).

The objective of this observational study is to assess the incidence rate of specific SAEs of interest (including fatalities) in patients with severe hepatic VOD post-HSCT treated with Defitelio. Specific SAEs of interest will be recorded by the treating physician or by the site staff, whether or not these are considered to be related to the treatment received.

MedDRA coding will be used to classify and tabulate SAEs. Frequencies (absolute and percentages) across System Organ Classes (SOC) and for individual events within those classes will be provided.

The focus on safety will be on particular serious events of interest, listed as identified or potential risks in the Risk Management Plan, namely haemorrhage, coagulopathy, hypotension, immunogenicity (allergic and hypersensitivity reactions), injection site reactions, infection and septicaemia, thromboembolic events, pregnancy and lactation. Incidence rates will be reported with 95% confidence intervals (CIs).

The following secondary endpoints will also be assessed: time to and rate of VOD and MOF resolution, Day +100 survival, and overall survival.

This is an observational study and all outcomes in this registry are only descriptive. As a result, no statistical comparisons will be made.

For each of the binary endpoints, statistics will be presented in terms of the rates of occurrence, with a 95% CI.

For analysis of survival time, measured from the date of HSCT until the date of event occurrence, data will be presented using Kaplan-Meier estimates. Patients who withdraw from the study for whatever reason will be censored at their date of withdrawal.

Milestones

Information to sites	April 2014
Start of data collection	April 2015
End of data collection	July 2019
Study progress reports	Yearly
Interim reports	Yearly (in concomitance with PSURs)
Final report of study results	July 2020

4. AMENDMENTS AND UPDATES

The present Version 2 has been updated from Version 1.3 to align information due to the study progress.

5. RATIONALE AND BACKGROUND

Defitelio® has been granted a Marketing Authorisation in Europe on 18 October 2013 under exceptional circumstances.

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

As a specific obligation (SOB), Gentium has been required to set up a disease registry to collect safety and outcome data, and to assess patterns of utilisation of Defitelio in the post-approval setting.

This is a multi-centre, multinational and prospective observational (non-interventional) disease registry of patients with severe hepatic VOD following HSCT and treated with Defitelio.

Gentium has been required to ensure that information regarding all potential or identified risks reported in the most recent version of the Risk Management Plan is being collected. The present protocol describes the disease registry as fulfillment of the SOB.

Hepatic VOD is one of the most common life-threatening regimen-related toxicities that constitute a barrier to successful allogeneic and autologous HSCT. VOD is characterised by rapid weight gain, painful hepatomegaly, hyperbilirubinemia/jaundice, and ascites/fluid retention, without other identifiable causes for liver disease (Richardson, 2012).

In the recent survey on 135 studies performed between 1997 and October 2007, the overall mean incidence of VOD in patients undergoing HSCT has been reported to be 13.7%, with a lower rate of 9.6 % when Baltimore criteria (more likely to capture the more severe forms of the disease) were applied (Coppell, 2010). Severe hepatic VOD, usually associated with pulmonary or renal dysfunction (i.e., multi-organ failure, MOF), with or without encephalopathy, and bearing a mortality rate of more than 80% by 100 days after HSCT, is reported to occur in about 40-60% of patients developing VOD.

The pathophysiology of VOD is multifactorial and complex. Both endothelial cell damage and prothrombotic-hypofibrinolytic state are critical factors in the pathophysiology of this disease. Antithrombotic and thrombolytic agents (with or without concurrent heparin) have been evaluated for the treatment of VOD but proved to be limited by significant toxicity, including fatal haemorrhage.

Defibrotide, developed by Gentium S.r.L, is a single-stranded polydeoxyribonucleotide derived from porcine intestinal mucosa by controlled depolymerisation.

In vitro, defibrotide has been shown to bind to various sites on vascular endothelium that are involved in cell regulation, providing a stimulus that promotes protection of activated endothelial cells. Defibrotide has also been shown to protect endothelial cells from fludarabine-mediated apoptosis, while not impacting its anti-leukemic effect. It is postulated that these actions protect endothelial cells. Also, in vitro, defibrotide has been shown to increase tissue-type plasminogen activator (t-PA) function and decrease plasminogen activator inhibitor-1 (PAI-1) activity resulting in a decrease in procoagulant activity and an increase in the fibrinolytic potential of endothelial cells.

During the clinical development programme, the efficacy and safety of Defitelio in the treatment of severe hepatic VOD have been studied in a pivotal Phase 3 historical controlled study (2005-01). Forty-four children and 58 adult patients with severe hepatic VOD post-HSCT, were treated with Defitelio 25 mg/kg/day by intravenous infusion, and compared with 32 historical control patients. Median length of therapy in those treated with Defitelio was 22 days.

A significantly higher proportion of patients in the Defitelio treated group achieved a complete response defined as total bilirubin less than 2 mg/dL and resolution of MOF; Day+100 complete response was 23.5% (24/102) with Defitelio versus 9.4% (3/32) in the historical control group (p=0.013). In addition, Day+100 survival rate was improved in the Defitelio group with 38.2% (39/102) of the patients surviving versus 25.0% (8/32) in the historical control group (p=0.034).

The efficacy data from this pivotal study are supported and confirmed with data from a dose-finding study (25 mg/kg/day arm) and the final data from the Treatment IND study (severe hepatic VOD subset), as presented in Table 1 and Table 2.

Outcome data available from 611 patients treated with Defitelio on a compassionate use basis for non-severe and severe hepatic VOD post-transplant, are also consistent with the controlled clinical studies, with complete response rate 24% (51/212) and survival 37% (78/212) in the subset of patients with severe hepatic VOD.

Table 1: Treatment Study Results: Complete Response of Severe Hepatic VOD at Day+100

	Individual Studies			
	Dose-Finding (25mg/kg/day arm)	**Open Label Treatment IND (25mg/kg/day)**	**Historically Controlled Trial (25mg/kg/day)**	
			Defibrotide treated group	**Historical Control**
Complete Response by Day+100	43% (32/75)	39.3% (201/512)	23.5% (24/102)	9.4% (3/32)
			p= 0.0131	

Table 2: Treatment Study results: Day+100 Survival

	Individual Studies			
	Dose-Finding (25mg/kg/day arm)	**Open Label Treatment IND (25mg/kg/day)**	**Historically Controlled Trial (25mg/kg/day)**	
			Defibrotide treated group	**Historical Control**
Survival by Day+100	43.9%*	49.5%*	38.2%*	25.0%*
			p=0.0341	

*= KM estimates for time-to-event analysis by Day+100

There was an insurmountable ethical problem with conducting a placebo-controlled study in this indication because, once severe hepatic VOD is established, there is a very immediate risk of death, and therefore the use of placebo in the context of the treatment study would have entailed the risk of irreversible harm to the patient, contrary to the EMEA/CHMP position statement on

use of placebo in clinical trials (2001) EMEA/17424/01 and the Declaration of Helsinki (59th WMA General Assembly, Seoul, Korea, October 2008).

An earlier attempt to conduct a controlled study in the treatment indication had to be abandoned after 3.5 years with only 20% of the patients recruited. This was due to the growing evidence of efficacy of Defitelio, the acceptance of this efficacy by the clinical experts with the consequent increasing lack of equipoise, and the availability of Defitelio on a compassionate use basis.

Therefore, safety and outcome data on the use of Defitelio in patients with severe hepatic VOD will be obtained in the present observational registry in real-life setting, when the decision on treatment resides with the treating physician in the patient's best interest.

6. RESEARCH QUESTION AND OBJECTIVES

The main objective of the registry is to assess the incidence rate of specific SAEs of interest (including fatalities) in patients with severe hepatic VOD post-HSCT treated with Defitelio.

Secondary objectives will be:

- To describe the population treated with Defitelio (age, gender, patients with pre-existing liver or severe renal insufficiency; patient with intrinsic lung disease)
- To determine the incidence rate of MOF and graft-versus-host disease (GvHD) in adult and paediatric patients receiving Defitelio
- To determine survival by Day+100 post-HSCT, overall survival and mortality due to VOD in patients treated with Defitelio
- To determine the rate of VOD and VOD with MOF resolution any time after treatment initiation in patients treated with Defitelio.

7. RESEARCH METHODS

7.1. Study Design

This is a multi-centre, multinational, prospective observational study, enrolling patients treated with Defitelio.

7.2. Setting

The registry will be performed in collaboration with the European Society for Blood and Marrow Transplantation (EBMT). Participating sites will be transplant centres that are members of EBMT resulting in the following countries being approached: Belgium, Czech Republic, Denmark, France, Hungary, Ireland, Italy, Bulgaria, Cyprus, Greece, Latvia, Slovakia, Austria, Norway, Lithuania, the Netherlands, Poland, Portugal, Spain, Sweden, UK, Croatia, Estonia, Iceland, Romania, Slovenia and Finland. Initially the only centres approached were ones conducting at least 100 transplants per year. However when the initial list of 46 sites were contacted only 22 agreed to participate, therefore the registry was opened up to any countries with a sufficient number of sites interested in participating, that are members of EBMT. Based on available literature, the incidence of severe hepatic VOD can be estimated to be 3-5% of patients undergoing HSCT. Given the extremely low incidence of the disease, and in order to collect meaningful clinical data, the present registry will be conducted in as many European transplant centres as possible so that a reasonable possibility exists that severe hepatic VOD occurs, and that patients with severe hepatic VOD may be allocated to treatment with Defitelio, according to patient´s best interest. The severe hepatic VOD diagnoses will be initially performed by the treating physician according to usual clinical practice.

During the inclusion period, physicians will be asked to complete a patient registration form recording all consecutive patients diagnosed with severe hepatic VOD post-HSCT and agreeing to take part in the study. In addition all patients prescribed Defitelio regardless of indication will also be registered, and information will be collected on the indication for which Defitelio has been administered.

There will not be any specific exclusion criteria; however contraindications, special warnings and precautions for use as detailed in the SPC will have to be considered by the treating physician.

After their inclusion, patient information will be collected from physician sites at 100 days, 6 months and 12 months post-HSCT. Physicians or delegate will collect data routinely monitored during clinical practice in the registry form and will describe changes in patient treatment and the occurrence of events during each specific data collection time period (see proposed e-Form in APPENDIX 1).

The inclusion of patients into the registry will be monitored every 3 months.

The treatment for severe hepatic VOD will be established based on the physician’s judgement and according to current clinical practice. As an observational study, this registry will not change the patient/physician relationship, nor influence the physician’s drug prescription or therapeutic management of the patient.

7.3. Variables

Patient History and Baseline Information:

- Patient demography: age, gender,
- Medical history:
  - primary diagnosis (e.g., leukaemia: AML, ALL, CML, others; inborn errors: OP, FMAS, others);
  - history of previous transplants
  - risk factors for VOD (prior abdominal irradiation, prior treatment with gemtuzumab, pre-existing liver diseases, impaired adrenal gland function, prior chronic hepatic, renal or intrinsic lung disease)
- Stem cell transplantation information: date of transplant, graft type (autologous/allogeneic), type of conditioning (myeloablative/non-myeloablative), matched/mismatched, GvHD prophylaxis (calcineurin inhibitors, ATG, sirolimus, others)
- Diagnosis of severe hepatic VOD:
  - date of onset, hyperbilirubinemia (Y/N), hepatomegaly (Y/N), ascites (Y/N), weight gain >5% (Y/N), RUQ pain (Y/N), liver histology (Y/N), other (Y/N)
  - Concurrent organ dysfunction: renal insufficiency (dialysis dependence if any), liver insufficiency, non-infectious lung dysfunction (ventilator dependence if any), encephalopathy, other.
- Current pregnancy or lactation (if applicable)

Relevant Treatment:

- Defitelio: start date, dose, duration (date of last administration), indication for use

Analysis Variables:

- SAEs of interest
  - haemorrhage and site of bleeding
  - hypotension
  - coagulopathy
  - allergic or hypersensitivity reactions
  - injection site reaction
  - infection, septicaemia
  - thromboembolic events
- Any SAEs, up to 12 months post-HSCT
- Pregnancy or lactation (if appropriate)

- Relevant concomitant medication: thrombolytic therapy; anticoagulant therapy (including direct thrombin and Xa inhibitors); corticosteroids
- Outcome data:
  - VOD/MOF resolution and time to resolution
  - patient alive (Y/N)- and survival time
  - date and cause of death

7.4. Data Sources

Data routinely collected during clinical practice will be entered by the treating physician in a registry-specific e-form (APPENDIX 1) to describe the severe hepatic VOD patient status at 100 days, 6 months and 12 months after HSCT. The registry-specific forms will be assessed for completeness on an ongoing-basis, and attempts to retrieve any missing information will be undertaken either via cross-reference to MED B form of the EBMT registry (identical patient ID code will be used as identifier) and via requests sent to the site. At the launch of the program, each participating centre will be informed and trained about the registry form, and asked to ensure the required data to be recorded in the patient file.

7.5. Sample Size

Study size is based on the number of available patients (who were treated with Defitelio) listed in the database (participating sites were notified to cease patient recruitment as of 18 July 2018) (n=163) after receiving positive opinion from the Committee for Medicinal Products for Human Use (CHMP) on 28 June 2018.

7.6. Data Management

ProMISe (Project Manager Internet Server) is the central data management system used by the EBMT and will be used for the collection of information in this registry. Access to the ProMISe is password protected through individual accounts and users are able to enter and retrieve data directly over a secure internet connection. All users access the same data repository but data visualisation is restricted to the user's centre data. The only software necessary is Internet Explorer, version 10 or higher.

When online, centres can access their centre database, to view, retrieve or enter individual patient data for their own centre. Users can also download their own centre database for reference purposes.

SOURCE: http://www.ebmt.org/Contents/Data-Management/Registrystructure/DatamanagementsystemProMIse/Pages/Data-management-system-ProMIse.aspx

The study data will be downloaded by the EBMT and will be provided to the Sponsor in data transfer file. The MAH, or a sub-contractor designated by the MAH, will use this data to create data files that can be analysed using SAS. Concomitant medications will be coded according to WHODrug. Medical history and SAEs of Special Interest will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA).

A final validation of the database will be performed and the database locked before statistical analysis is conducted.

7.7. Data Analysis

7.7.1. Analysis Population

The Study Population is defined as the population of patients with severe hepatic VOD post-HSCT who are entered into the registry and treated with Defitelio. This population will be used for all summaries. The initial diagnosis of severe hepatic VOD will be performed by the treating physician according to clinical practice. The relevant sections of the e-form will be filled in accordingly.

Patients treated with Defitelio for reasons other than severe hepatic VOD post-HSCT who are entered into the registry will be summarised as noted in Section 7.7.2.4.

7.7.2. Statistical Analysis

Statistical analysis will be carried out using SAS software, version 9.2 or later.

7.7.2.1. Baseline Evaluation

Baseline data will be summarised. For continuous variables such as age, summary statistics will include number of patients (n), mean, median, standard deviation and range (minimum – maximum). For binary and categorical data, such as gender and primary diagnosis, summary statistics will include n and frequency (absolute and percentage).

7.7.2.2. Safety Evaluation

The main objective of the study is to evaluate the rate of SAEs of interest across the Defitelio treated group. All SAEs of interest will be recorded by the treating physician or by the site staff, whether or not these are considered to be related to the treatment received.

MedDRA coding will be used to classify and tabulate SAEs. Frequencies (absolute and percentages) across SOC and for individual events within those classes will be provided.

Safety data will be obtained by collecting the SAEs of interest, those listed as identified and potential risks in the Risk Management Plan, namely haemorrhage, hypotension, coagulopathy, immunogenicity (allergic and hypersensitivity reactions), injection site reactions, infection and septicaemia, thromboembolic events, pregnancy and lactation.

Incidence rates will be calculated with 95% CIs.

7.7.2.3. Outcome Evaluation

There are several endpoints of interest in relation to clinical outcome:

- Time to and rate of VOD and MOF resolution
- Survival at Day+100 post-HSCT and overall survival

This is an observational study and all outcomes in this registry are only descriptive. As a result, no statistical comparisons will be made. For each of the binary endpoints, statistics will be

presented in terms of incidence rate with a 95% CI. For survival time, measured from the date of HSCT until the date of outcome occurrence, data will be presented using Kaplan-Meier estimates. Patients who withdraw from the study for whatever reason will be censored at their date of withdrawal.

7.7.2.4. Other Analyses

Particular subgroups of interest, including age (<18 years, ≥18 years) and gender, will be pre-specified in the Statistical Analysis Plan and the rates of MOF and VOD resolution and Day+100 survival together with 95% CIs, calculated for those subgroups.

Other uses of Defitelio in the scope of transplantation will be described with regard to the indications, and data will be presented in summary tables.

7.7.2.5. Interim analyses

It was envisaged that interim analyses will be performed each year. However, due to the slow recruitment rate and due to challenges of recruiting into a control arm (i.e., complete absence of control patients), interim analysis is not feasible.

A final study analysis comprising of the study population, as defined above, will be described and the baseline, safety and outcome analyses will be performed on the overall study population.

7.8. Quality control

The data provided in this study will be checked for inconsistencies and potential errors at the time it is received by the MAH (or designate) from the EBMT.

No onsite monitoring will be possible but EBMT will perform remote monitoring calls for data quality checking in 10% of total sites dependent on an escalated monitoring procedure which considers the compliance of each site with study procedures. The aim of these telephone monitoring visits will be to check the correct reporting of adverse reactions according to the protocol and communicate with the physician. These monitoring calls will also enable EBMT to resolve any administrative issues, potential logistical problems raised by the physician and to discuss the recruitment of patients and compliance.

For any subject who cannot be contacted at 1-year post-HSCT, the site will make documented attempts to contact the subject, by phone or letter, and make reasonable efforts to confirm that the subject is not dead.

8. PROTECTION OF HUMAN SUBJECTS

The study will be conducted in compliance with the present protocol, Good Epidemiology Practice guidelines, the ethical principles arising from the Declaration of Helsinki revised in 2013, and all current local regulations, where applicable.

Participating physicians are assured by the initiator of the study that it will be conducted in accordance with the provisions of the above regulations and principles and that it will meet current laws and practices.

The data collected during the study will be obtained from medical notes on each patient.

The study will not alter the treatment management of the patients and no invasive procedures or special surveillance measures are required by the protocol.

It will be the responsibility of the physician to fully inform each subject and provide adequate explanation of the aims and methods of the registry, and to obtain written informed consent for personal and medical data collection. For subjects not qualified or incapable of giving legal consent, consent will be obtained from the legally acceptable representative (if permitted by local regulations).

The confidentiality of the patient data stored in the EBMT Registry is of paramount importance to the EBMT and procedures are in place to ensure the data is transferred and stored with the highest possible level of security. In addition to the above, the transfer or storage of confidential patient data must abide by the law in each country.

As the EBMT is registered as a Dutch foundation, Dutch law applies to the EBMT and it abides by the implementation of the European Union (EU) directive (95/46/EC), regulating how personal data is to be handled, through the Dutch application of this law.

The law regulating transfer of data within the EU does not cover countries outside EU/EEA (European Economic Area), and the EBMT must ensure that centres lying outside this zone agree to conform to the EU law as stated above. The Registry retains the right to request that centres lying outside the EU/EEA return the completed European Union Regulations statement on data protection.

In addition, if the centre intends to forward data, either directly or through the EBMT, to countries located outside the EU/EEA, they must ensure this is explicitly stated in the patient consent form. It is the centre's responsibility to ensure that the patient has consented before data is forwarded to the EBMT.

Source: http://www.ebmt.org/Contents/Data-Management/Dataconfidentiality/Pages/Data-confidentiality.aspx

9. REPORTING OF SPONTANEOUSLY OBSERVED SAES AND SERIOUS ADVERSE DRUG REACTIONS

9.1. Definition

SAE: any untoward medical occurrence associated with the use of a medicinal product in humans, whether or not considered related, that meets one or more of the Seriousness criteria listed below:

- Death (only if the Adverse Event is considered to be the cause of Death)
- Life-threatening (i.e., immediate risk of death),
- In-patient hospitalization or prolongation of existing hospitalization,
- Persistent or significant disability/incapacity,
- Congenital anomaly/birth defect,
- Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Serious Adverse Drug Reaction: any SAE for which there is a reasonable possibility that the medicinal product caused the adverse event. The event cannot be explained by other factors such as the subject's clinical condition, pre-existing/intercurrent illness, concomitant medication, etc.

Relationship: grading used to describe the relationship of SAE to Defitelio or alternative treatment:

- Not Related: the event can be explained by other factors such as the subject's clinical condition, pre-existing/intercurrent illness, concomitant medication, etc. Nonetheless, a conservative approach to causality assessment will be taken, and adverse events will be carefully considered independently of the causality assessment indicated by the physician.
- Related: there is a reasonable possibility that the medicinal product (Defitelio or alternative treatment) caused the adverse event (e.g., laboratory test abnormality follows a reasonable temporal sequence from the time of drug administration; dechallenge and rechallenge information are indicative of a drug related event)

Action taken: Action taken with medicinal product (Defitelio or alternative treatment) due to the event which bases on the following grades:

- None/Dose not changed
- Drug withdrawn

Outcome: Outcome of SAE based on the following criteria:

- Death (only if the Adverse Event term reported is considered to be the cause of Death. Please note: for consistency, if outcome is 'Death' also seriousness must be 'Death')
- Recovered/resolved
- Recovered with *sequelae*
- Recovering/resolving
- Not Recovered/resolved: the event does not resolve

9.2. Recording, Assessment and Reporting of Adverse Events

During the overall follow-up period of the study (up to 12 months after HSCT), physicians participating in the study will be instructed to report any spontaneously observed SAEs that occur among patients treated with Defitelio within 24 hours from the time the physician is made aware of the SAE using a designated SAE Reporting Form.

The SAE Form will include an assessment of the potential causal relationship between use of Defitelio (or any alternative treatment) and the occurrence of the event in addition to a description of the event seriousness, outcome and concomitant medications used at the time of event occurrence.

A printed and signed copy of the SAE form will be sent to the contact information provided on the SAE form.

All SAEs, whether initial or follow-up reports, must always be accompanied by a narrative of the event. Reporters may be contacted with follow-up questions in case of missing important information.

Reporting: Serious adverse drug reactions will be expedited to EU regulators as appropriate by Jazz Pharmaceuticals (on behalf of the MAH Gentium S.r.L).

10. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

A final study report, including the statistical and clinical evaluations, will be prepared under the responsibility of the EBMT and Jazz Pharmaceuticals on behalf of Gentium S.r.L.

The results of the study will be submitted for publication and/or presented at scientific meetings after completion of the final study report under the responsibility of Jazz Pharmaceuticals (on behalf of the MAH Gentium S.r.L) or EBMT.

Being a multi-centre study, the first publication should be a joint-paper, reporting the combined results from all the centres.

It is agreed that before the publication, Jazz Pharmaceuticals (on behalf of the MAH Gentium S.r.L) or EBMT (as appropriate) will be given 30 days to review and comment upon the manuscript.

Jazz Pharmaceuticals (on behalf of Gentium S.r.L) shall submit updates of the study to national and international Regulatory Authorities in fulfilment of its Regulatory commitments.

11. 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: 157-168.

Richardson PG, Ho VT, Giralt S, et al. Safety and efficacy of defibrotide for the treatment of severe hepatic veno-occlusive disease. Ther Adv Hematol 2012; 3(4): 253-265.

APPENDIX 1

e-FORM

Defitelio® – European Disease Registry Program (DF VOD-2013-03-REG)
REGISTRATION FORM

CENTRE IDENTIFICATION

Med-AB code _____ _____
Centre Patient Number

Hospital:……Unit:……

Contact person:…….. ……

Phone:……. Fax:…….

e-mail:……..

PATIENT DATA

Date of this report: _____/___/___

Informed consent obtained
☐ YES ☐ NO →If no, Data collection cannot proceed

Hospital Unique Patient Number or Code:_____

Patient study identification number: __ __ __ __ __ __

Initials*: ____//____(first name(s)//family name(s))

Date of birth**: _____/___/___

Gender: ☐ Male ☐ Female

Weight (kg): _____

*To be completed only if the local regulations allow to collect the patient's initials

**At least year and month; according to local regulation,, full birthdates cannot be recorded in some countries

PRIMARY DISEASE

Date of initial diagnosis: _____/___/___

PRIMARY DISEASE DIAGNOSIS:……..

DIAGNOSIS OF VOD

Diagnosis of VOD ☐ YES ☐ NO

Date of the Diagnosis _____/___/___ (

Severe VOD ?
☐ YES ☐ NO

HSCT

Chronological number of HSCT for this patient _____

If >1,
date of last HSCT before this one_____/___/___
(

type of last HSCT before this one
☐ Allo ☐ Auto ☐ Unknown

Date of current HSCT: _____/___/___

Type of current HSCT:
☐ Autologous ☐ Allogeneic

Preparative (conditioning) regimen given?
☐ YES ☐ NO

Conditioning start date: _____/___/___

Was conditioning myeloablative?
☐ YES ☐ NO

VOD DIAGNOSTIC CRITERIA

Bilirubin >2 mg/dl ☐ YES ☐ NO
Weight gain >5% ☐ YES ☐ NO
Ascites ☐ YES ☐ NO
Hepatomegaly ☐ YES ☐ NO
Liver histology ☐ YES ☐ NO

MULTIORGAN FAILURE

☐ YES ☐ NO

If Yes:
Renal ☐ YES ☐ NO
If Yes, Dialysis ☐ YES ☐ NO

RUQ pain ☐ YES ☐ NO other ☐ YES ☐ NO *(Specify):*……..	Respiratory ☐ YES ☐ NO If Yes, Assisted Ventilation ☐ YES ☐NO Cerebral ☐ YES ☐ NO Other ☐ YES ☐ NO Specify:
TREATMENT FOR VOD Defitelio® ☐ Supportive care only ☐ Alternative sVOD treatment ☐ → *Specify* _____	**REASON for DEFITELIO® ADMINISTRATION** ☐ Treatment of severe VOD ☐ Other than treatment for severe VOD (*specify*)……..…….
	DEFITELIO® IV ADMINISTRATION FOR VOD Start Date _____/___/___ Daily dose (mg/kg/day)_____

Comments to the Registration Form

CIC number of the 1st HSCT when known : _ _ _ _ _ _ _ _
Patient Number in MEDAB : _ _ _ _ _ _ _ _
Comment to Registration Form : _

Defitelio® – European Disease Registry Program (DF VOD-2013-03-REG)

FOLLOW-UP 100 DAYS POST-HSCT

PATIENT STATUS AT LAST CONTACT

Relapse ☐ YES ☐ NO Date of relapse _____
DLI ☐ YES ☐NO, If yes, date of 1st DLI (Donor Lymphocyte Infusion)_____
Has VOD been diagnosed since last visit? ☐ YES ☐NO (for off label use or if absent at registration)
Survival Status: Alive ☐ Dead ☐ Died before HSCT but after start conditioning ☐
Date of follow-up (last contact or Date of death): _____/___/___
Main cause of Death *(check only one main cause):*

Relapse or progression/persistent disease ☐
Secondary malignancy ☐
HSCT related cause *(check as many as appropriate)* ☐

GvHD ☐ YES ☐ NO Cardiac toxicity ☐ YES ☐ NO Rejection/poor graft function ☐YES ☐NO
Infection ☐ YES ☐ NO Pulmonary Toxicity ☐ YES ☐ NO Renal Toxicity ☐ YES ☐ NO
VOD ☐ YES ☐ NO Other: ☐ YES ☐NO
*Specify*_____

Cell therapy (non HSCT) related ☐
Unknown ☐
Other ☐ *Specify*_____

DEFITELIO® ADMINISTRATION

Defitelio® administration status?
☐ Ongoing treatment ☐ Completed (permanent withdrawal)

If completed: Date of last infusion?
_____/___/___

Temporary withdrawal since registration form?
☐ YES ☐ NO
If temporary withdrawal, Total No.days of withdrawal? _ _ _ _

Reason for stopping treatment: **temporary or permanent*
VOD resolution ☐ YES ☐ NO
No improvement ☐ YES ☐ NO
Death ☐ YES ☐ NO
Hospital discharge ☐ YES ☐ NO
Untoward reaction to Defitelio®
☐ YES ☐ NOSpecify:
_____
Other ☐ YES☐NO

ANY SERIOUS ADVERSE EVENTS (SAEs) since last visit?

☐ NO
☐ YES

if YES complete in detail the SAE FORM and SEND A FAX OR A SCANNED COPY TO THE CONTACT INFORMATION LISTED ON THE SAE FORM

Specify: _____	
CLINICAL RESPONSE VOD RESOLUTION ☐ YES ☐ NO If yes, Date: _____/___/___ Did MOF developed after patient registration? ☐ YES ☐ NO MOF RESOLUTION ☐ YES ☐ NO Renal : ☐ YES ☐NO Date_____/___/___ Respiratory: ☐ YES ☐NO Date_____/___/___ Cerebral: ☐ YES ☐NO Date_____/___/___ Other: ☐ YES ☐NO Date_____/___/___	**ACUTE GRAFT-*versus*-HOST-DISEASE** ☐ NO ☐ YES If yes, Date of diagnosis: _____/___/___ Maximum grade of acute GvHD: ☐ I ☐ II ☐ III ☐ IV

SERIOUS ADVERSE EVENTS OF INTEREST

Did a SAE of interest occur since last visit? ☐ YES ☐ NO

Sequence number of the SAE of interest : ___

Date SAE of interest started? _ _ _ _ / _ _ / _ _

Bleeding ☐ Site:_____

Hypotension ☐

Coagulopathy ☐

Allergic/Hypersensitivity reactions ☐

Injection site reaction ☐

Infection ☐ Site: _____

Thromboembolic events ☐

If any Yes, please complete in detail the SAE FORM and submit to the Drug Safety Department

**if several episodes please indicate each date*

PREGNANCY*	LACTATION	CONCOMITANT MEDICATIONS ☐ YES ☐ NO
☐ YES ☐ NO *If Yes is selected, please also complete and submit the pregnancy form	☐ YES ☐ NO	Sequence number of the concomitant medication : ___ Medicinal product _ _ _ _ _ _ _ Medicinal product daily dose? _ _ _ _ _ Medicinal product unit? _ _ _ _ Medicinal product duration (in days)? _ _ _ Medicinal product indication _ _ _ _ **if several please indicate each*

Comments

CIC number of the 1st HSCT when known : _ _ _ _ _ _ _ _

Patient Number in MEDAB : _ _ _ _ _ _ _ _

Comment to the Follow-up Forms at 100 days : _

Defitelio® – European Disease Registry Program (DF VOD-2013-03-REG)
FOLLOW-UP 6-MONTHS/12 MONTHS POST HSCT

☐ 6 months ☐ 12 months

PATIENT STATUS AT LAST CONTACT

Relapse ☐ YES ☐ NO Date of relapse_____
DLI ☐ YES ☐NO, If yes, date of 1st DLI (Donor Lymphocyte Infusion)_____
Has VOD been diagnosed since last visit? ☐ YES ☐NO *(for off label use or absent at previous follow-up)*
Survival Status Alive ☐ Dead ☐ Lost to Follow-up ☐
Date of follow-up (last contact or Date of death): _____/___/___
Main cause of Death *(check only one main cause)*
Relapse or progression/persistent disease ☐
Secondary malignancy ☐
HSCT related cause *(check as many as appropriate)* ☐
☐ ☐

GvHD ☐ YES ☐ NO
Infection ☐ YES ☐ NO
VOD ☐ YES ☐ NO
Cardiac toxicity ☐ YES ☐ NO
Pulmonary Toxicity☐ YES ☐ NO
Other: ☐ YES ☐ NO
*Specify:*_____
Rejection/poor graft function ☐YES ☐ NO
Renal Toxicity ☐ YES ☐ NO

Cell therapy (non HSCT) related ☐
Unknown ☐
Other ☐ *Specify*_____

DEFITELIO® ADMINISTRATION
(Fill this Section if Defitelio administration continued after Day+100 post-HSCT)

Defitelio® administration status?
☐ Ongoing treatment ☐ Completed (permanent withdrawal)

If completed: Date of last infusion?
_____/___/___

Temporary withdrawal since registration form?
☐ YES ☐ NO

If temporary withdrawal, Total No.days of withdrawal? _ _ _ _

Reason for stopping treatment: **temporary or permanent* VOD resolution ☐ YES ☐ NO
No improvement ☐ YES ☐ NO
Death ☐ YES ☐ NO

ANY SERIOUS ADVERSE EVENTS since last visit (SAEs)?

☐ NO ☐ YES

if YES complete in details the SAE FORM and SEND A FAX OR A SCANNED COPY TO THE CONTACT INFORMATION LISTED ON THE SAE FORM

Hospital discharge ☐ YES ☐ NO
Untoward reaction to Defitelio®
☐ YES ☐ NO
Specify: _____
☐ Other ☐ YES ☐ NO
Specify: _____

CLINICAL RESPONSE

☐ VOD RESOLUTION ☐ YES ☐ NO
Date: _____/___/___
Did MOF developed after patient's last follow-up? ☐ YES ☐ NO
☐ MOF RESOLUTION ☐ YES ☐ NO
☐ Renal Date_____/___/___
☐ Respiratory Date_____/___/___
☐ Cerebral Date_____/___/___
☐ Other Date_____/___/___

ACUTE GRAFT-*versus*-HOST-DISEASE

☐ NO ☐ YES If Yes: Date of diagnosis: __/___/___

Maximum grade of acute GvHD: ☐ I ☐ II ☐ III ☐ IV

CHRONIC GRAFT-*versus*-HOST-DISEASE

☐ NO ☐YES
If Yes: Date of diagnosis: _____/___/___
Organ(s) involved:
Eyes ☐ Gastrointestinal tract ☐Lungs ☐Oral cavity ☐
Liver ☐ Skin ☐Other ☐: _ _ _ _ _ _ _

SERIOUS ADVERSE EVENTS OF INTEREST

Did a SAE of interest occur since last visit? ☐ YES ☐ NO
Sequence number of the SAE of interest : ___
Date SAE of interest started? _ _ _ _ / _ _ / _ _
Bleeding ☐ Site:_____
Hypotension ☐
Coagulopathy ☐ Allergic/Hypersensitivity reactions ☐
Injection site reaction ☐
Infection ☐
Site: _____
Thromboembolic events ☐
If any Yes, please complete in detail the SAE FORM and submit to the Drug Safety Department
**if several episodes please indicate each date*

PREGNANCY*
☐ YES ☐ NO
*If Yes is selected, please also complete and submit the pregnancy form

LACTATION
☐ YES ☐ NO

CONCOMITANT MEDICATIONS ☐ YES ☐ NO
Sequence number of the concomitant medication : ___
Medicinal product _ _ _ _ _ _ _
Medicinal product daily dose? _ _ _ _ _
Medicinal product unit? _ _ _ _
Medicinal product duration (in days)? _ _ _
Medicinal product indication _ _ _ _
**if several please indicate each*

Comments

CIC number of the 1st HSCT when known : _ _ _ _ _ _ _ _
Patient Number in MEDAB : _ _ _ _ _ _ _ _
Comment to the Follow-up Forms at 6 or 12 months : _

Protocol: DF VOD-2013-03-REG
Summary of Changes

Title	A multi-centre, multinational, prospective observational registry to collect safety and outcome data in patients diagnosed with severe hepatic veno-occlusive disease (VOD) following haematopoietic stem cell transplantation (HSCT) and treated with Defitelio®
Protocol version identifier	DF VOD-2013-03-REG, Version 2
Date protocol	28 November 2018
EU PAS register number	ENCEPP/SDPP/5592
Active substance	Defibrotide (ATC code B01AX01)
Medicinal product	Defitelio
Product reference	EU/1/13/878
Procedure number	EMEA/H/C/002393
Marketing authorisation holder	Gentium S.r.L PiazzaXX Settembre 2 Villa Guardia 22079 Italy
Joint PASS	No
Author	[redacted] Jazz Pharmaceuticals, Inc. 3180 Porter Drive Palo Alto, CA 94304 Telephone: +1 650 496 3777 [redacted]

SUMMARY AND JUSTIFICATION OF CHANGES

As a specific obligation (SOB), Gentium S.r.L (the Marketing Authorisation Holder [MAH] for Defitelio®) was required to set up a disease registry to collect safety and outcome data, and to assess patterns of utilisation of Defitelio in the post-approval setting. Accordingly, Protocol DF VOD-2013-03-REG is being conducted as a multi-centre, multinational, and prospective observational disease registry of patients with severe hepatic veno-occlusive disease (VOD) following haematopoietic stem cell transplant (HSCT) based on the European Blood and Marrow Transplantation (EBMT) registry system, to record patients treated with Defitelio or supportive care (control group).

On 4 August 2017, the MAH submitted to the Committee for Medicinal Products for Human Use (CHMP) an application for a type II variation (procedure no. EMEA/H/C/002393/II/0027) along with an updated risk management plan (RMP) version 4.0 in order to remove the control arm, cease patient recruitment in the study and to re-classify the Protocol DF VOD-2013-03-REG from a Category 2 study in the RMP (SOB) to a study listed as a Category 3 (required additional pharmacovigilance activities). On 28 June 2018, the MAH received a positive opinion from the CHMP on the submitted type II variation application with a recommendation to cease patient recruitment into the Protocol DF VOD-2013-03-REG upon approval of the variation (June 2018) and to provide the data collated from the registry as a Category 3 Post-Authorisation Measure within 1 year of last patient last visit.

Protocol DF VOD-2013-03-REG Version 2 is a significant amendment to Protocol DF VOD-2013-03-REG Version 1.3, previously dated 10 June 2016. The rationale for the significant changes was to revise content (including dates of registry milestones) in order to reflect ceasing of patient recruitment, and in order to remove the control arm from the study design. Other changes to the protocol include administrative and editorial changes. Major changes are summarised below:

- The Title of the Study, Rationale and Background, Research Question and Objectives, and Research Methods (Study Design, Variables, Sample Size, and Data Analysis) sections were updated in order to remove description of the control arm from the study.
- The list of active countries for the registry was revised for accuracy.
- The dates of registry milestones were updated in order to reflect ceasing of patient recruitment.
- Content throughout the protocol was updated in order to remove description of use of an independent reviewer to review diagnosis of severe hepatic VOD for the final populations of patients treated with Defitelio prior to interim and final analyses. This is because in the absence of a control arm, concordance between primary investigator and independent reviewer is not necessary.

Signature Manifestation

[redacted]
Date: Tuesday, 04 December 2018, 06:20 AM Pacific Time
Meaning: No further changes required. Accepted.
==========

[redacted]
Date: Tuesday, 04 December 2018, 07:46 AM Pacific Time
Meaning: No further changes required. Accepted.
==========

[redacted]
Date: Tuesday, 04 December 2018, 08:52 AM Pacific Time
Meaning: No further changes required. Accepted.
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[redacted]
Date: Tuesday, 04 December 2018, 09:59 AM Pacific Time
Meaning: No further changes required. Accepted.
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