

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208114Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA/BLA # 208114
Product Name: Defitelio (defibrotide sodium)

PMR/PMC Description: Conduct an analysis of safety in a randomized, open-label multi-center clinical trial comparing defibrotide versus best supportive care in the prevention of hepatic veno-occlusive disease in adult and pediatric patients, including all adverse events, laboratory abnormalities and frequent peri-infusion vital signs.
PMR# 3056-1

PMR/PMC Schedule Milestones:	Final Protocol Submission:	05/2016
	Trial Completion:	07/2021
	Final Report Submission:	01/2022

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Hepatic veno-occlusive disease (VOD) with multiorgan failure (MOF) is a rare and fatal complication of stem cell transplantation. The approval of defibrotide is based on an improvement in survival of patients with hepatic VOD and MOF in comparison to historical controls, but the patient population is clinically complex, and there is concern that the profile of nonfatal safety events may not be clear. There are currently no drugs approved for treatment of this disease, so based on the extreme unmet need in this population and the apparent survival benefit with defibrotide, it was deemed appropriate to obtain additional safety information in a post-marketing trial.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The approval of defibrotide is based on an improvement in survival of patients being treated for hepatic VOD and MOF in comparison to historical controls, but this patient population is clinically complex, and there is concern that the profile of nonfatal safety events may not be clear. The proposed PMR is to characterize the safety of defibrotide in a phase 3, randomized, open-label multi-center study comparing the efficacy of defibrotide versus best supportive care in the prevention of hepatic VOD in adult and pediatric patients. The protocol population will be clinically less complex (no MOF at study entry), and as such the analysis of safety is expected to be less confounded.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A phase 3, randomized, open-label multi-center study comparing defibrotide versus best supportive care in the prevention of hepatic VOD in adult and pediatric patients. The study will collect all adverse events, laboratory test results and frequent peri-infusional vital signs.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

Dose-response study or clinical trial performed for effectiveness

Nonclinical study, not safety-related (specify)

Other

5. Is the PMR/PMC clear, feasible, and appropriate?

Does the study/clinical trial meet criteria for PMRs or PMCs?

Are the objectives clear from the description of the PMR/PMC?

Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

There is a significant question about the public health risks of an approved drug

There is not enough existing information to assess these risks

Information cannot be gained through a different kind of investigation

The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

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/s/

BEATRICE A KALLUNGAL
03/25/2016

BARRY W MILLER
03/25/2016

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

NDA/BLA # **NDA 208114**
Product Name: **Defitelio (defibrotide sodium)**

PMC #2 Description: Develop a sensitive and specific anti-drug (defibrotide) binding and
neutralizing assay. Submit validation reports on the assay in a final report to
PMC# 3056-2 the NDA.

PMC Schedule Milestones: Submission of Final Binding (total ADA) Assay
Validation Report: 01/2017
Submission of NAb Assay Validation Report: 01/2021

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

The applicant needs to develop and validate anti-drug (defibrotide) binding and neutralizing methods and long-term data needed and therefore these studies are only feasible to conduct post-approval.

2. Describe the particular review issue and the goal of the study.

Defibrotide is a deoxyribonucleic acid derivative belong to oligonucleotide therapies, structurally related to DNA which can potentially display immunogenicity activity and may cross-react with endogenous DNA. The potential of immunogenicity of the product (defibrotide) in humans was not evaluated in the NDA. The goal of the study is to develop and validate anti-drug binding and neutralizing methods.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- X Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

The applicant committed to development and validation of screening and neutralizing methods for immunogenicity studies.

5. To be completed by ONDQA/OBP Manager:

- x Does the study meet criteria for PMCs?
- x Are the objectives clear from the description of the PMC?
- x Has the applicant adequately justified the choice of schedule milestone dates?
- x Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

NDA/BLA # **NDA 208114**
Product Name: **Defitelio (defibrotide sodium)**

PMC #3 Description: Evaluate patients' sera for binding and neutralizing antibodies to defibrotide
PMC# 3056-3 using the validated assay from PMC#2 and patient samples from a randomized, open-label multi-center clinical trial comparing defibrotide versus best supportive care in the prevention of hepatic veno-occlusive disease in adult and pediatric patients, and submit the data in a final immunogenicity study report.

PMC Schedule Milestones:	Final Protocol Submission:	<u>04/2016</u>
	Final Trial Completion:	<u>07/2021</u>
	Final Immunogenicity Report Submission:	<u>01/2019</u>
	Other: <u>Initial Protocol Submission:</u>	<u>01/2016</u>

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
 Long-term data needed (e.g., stability data)
 Only feasible to conduct post-approval
 Improvements to methods
 Theoretical concern
 Manufacturing process analysis
 Other

To conduct immunogenicity studies, long-term data and samples needed and therefore these studies are only feasible to conduct post-approval.

2. Describe the particular review issue and the goal of the study.

Defibrotide is a deoxyribonucleic acid derivative belong to oligonucleotide therapies, structurally related to DNA which can potentially display immunogenicity activity and may cross-react with endogenous DNA. The potential of immunogenicity of the product (defibrotide) in humans was not evaluated in the NDA. The goal of the study is to understand potential of inducing immunogenicity following administration of defibrotide by testing patients' sera with validated anti-drug binding and neutralizing methods.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- X Other

Describe the agreed-upon study:

(b) (4)

5. To be completed by ONDQA/OBP Manager:

- x Does the study meet criteria for PMCs?
- x Are the objectives clear from the description of the PMC?
- x Has the applicant adequately justified the choice of schedule milestone dates?
- x Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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/s/

BEATRICE A KALLUNGAL
03/25/2016

BARRY W MILLER
03/25/2016

Rare Pediatric Disease Priority Review Voucher eligibility checklist

Under section 529 of the Food, Drug, and Cosmetic Act, the sponsor of a human drug application (as defined in section 735(1) of the FD&C Act) for a rare pediatric disease drug product may be eligible for a voucher that can be used to obtain a priority review for a subsequent human drug application submitted under section 505(b)(1) of the FD&C Act or section 351 of the Public Health Service (PHS) Act after the date of approval of the rare pediatric disease drug product.

This checklist is intended to help determine if an NDA or BLA is eligible for a **Rare Pediatric Disease Priority Review Voucher**.

NDA/BLA	Review Division
NDA 208114 Defitelio (defibrotide)	DHP
Requirement	Meets? (yes/no)
For prevention or treatment of a <i>rare pediatric disease?</i> (<i>OOPD makes determination</i>)	No (determined by OOPD 3/21/16)
Contains no active ingredient (including any ester or salt of the active ingredient) that has been previously approved in any other application under section 505(b)(1), 505(b)(2), or 505(j) of the FD&C Act or section 351(a) or 351(k) of the PHS Act?	Yes (listed as NME in DARRTS)
FDA deems eligible for priority review?	yes (9/17/15 filing meeting)
Submitted under section 505(b)(1) (includes 505(b)(2) applications) of the FD&C Act or section 351(a) of the Public Health Service Act?	yes (9/17/15 filing meeting)
Relies on clinical data derived from studies examining a pediatric population and dosages of the drug intended for that population?	yes
Does not seek approval for an adult indication in the original rare pediatric disease product application?	yes (DEFITELIO is indicated for the treatment of adult and pediatric patients with hepatic veno-occlusive disease (VOD), also known as sinusoidal obstruction syndrome (SOS), with renal or pulmonary dysfunction following hematopoietic stem-cell transplantation (HSCT).)

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/s/

LARRY J BAUER
03/21/2016

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: 3/15/16

To: Beatrice Kallungal, Senior Regulatory Health Project Manager
Division of Hematology Products (DHP)

From: Rachael Conklin, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Through: Kathleen Davis, Team Leader, OPDP

Subject: Comments on draft labeling (Package Insert, Carton/Container Labeling) for DEFITELIO (defibrotide sodium) injection, for intravenous use
NDA 208114

In response to your labeling consult request dated September 16, 2015, we have reviewed the draft Package Insert (PI), draft Carton labeling, and draft Container labeling for DEFITELIO (defibrotide sodium) injection, for intravenous use (Defitelio). This review is based upon the version of the draft PI and Carton/Container labeling e-mailed to OPDP on March 10, 2016.

If you have any questions, please contact Rachael Conklin at (240) 402-8189 or Rachael.Conklin@fda.hhs.gov.

Prescribing Information

12.2 Pharmacodynamics

1. *“Mean PAI-1 levels on Days 7 and 14 were lower than those at baseline in patients with complete response (CR) and in those who were alive at Day+ 100, but this trend did not reach statistical significance”*

OPDP is concerned that the sponsor may use this sentence to support a descriptive data-based presentation in promotion, implying that this trend in PAI-1 levels is a reliable indicator of efficacy and can be used by prescribers to predict survival and/or complete response. With this in mind, is this information necessary/clinically significant for prescribers to understand the efficacy or safe use of the product? If this information is not essential for prescribers' comprehension of the effective and safe use of defibrotide, OPDP recommends deleting this sentence due to these potential promotional concerns.

Carton/Container Labeling:

OPDP acknowledges and concurs with the December 14, 2015, review of the carton and container labeling by the Division of Medication Error Prevention and Analysis (DMEPA) and has no additional comments on the carton and container labeling.

11 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS)
immediately following this page

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/s/

RACHAEL E CONKLIN
03/15/2016

REGULATORY PROJECT MANAGER PHYSICIAN LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 208114

Application Type: New NDA

Drug Name(s)/Dosage Form(s): Defitelio (defibrotide) 200 mg/2.5 mL solution

Applicant: Gentium S.p.A. (a Jazz Pharmaceuticals company)

Receipt Date: July 31, 2015

Goal Date: March 31, 2016

1. Regulatory History and Applicant's Main Proposals

Gentium S.p.A., a Jazz Pharmaceuticals company, submitted a New Drug Application 208114 for defibrotide with a proposed indication for the treatment of hepatic veno-occlusive disease (VOD), also known as sinusoidal obstruction syndrome (SOS), (b) (4) following hematopoietic stem cell transplant (HSCT).

Defibrotide is a new molecular entity being reviewed under the PDUFA V Program.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements of Prescribing Information (SRPI)" checklist (see Section 4 of this review).

3. Conclusions/Recommendations

No SRPI format deficiencies were identified in the review of this PI.

Selected Requirements of Prescribing Information

4. Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix for a sample tool illustrating Highlights format.

HIGHLIGHTS GENERAL FORMAT

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

- YES** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.

Comment:

- YES** 3. A horizontal line must separate:
- HL from the Table of Contents (TOC), **and**
 - TOC from the Full Prescribing Information (FPI).

Comment:

- YES** 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.

Comment:

- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix for HL format.

Comment:

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

- YES** 7. Headings in HL must be presented in the following order:

Heading	Required/Optional
• Highlights Heading	Required

Selected Requirements of Prescribing Information

• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a BOXED WARNING is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state “None.”)
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to five labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading, “**HIGHLIGHTS OF PRESCRIBING INFORMATION**” must be **bolded** and should appear in all UPPER CASE letters.

Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: “**These highlights do not include all the information needed to use (insert NAME OF DRUG PRODUCT) safely and effectively. See full prescribing information for (insert NAME OF DRUG PRODUCT).**” The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

- YES** 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.

Comment:

- N/A** 13. The BW must have a title in UPPER CASE, following the word “**WARNING**” and other words to identify the subject of the warning. Even if there is more than one warning, the term

Selected Requirements of Prescribing Information

“WARNING” and not “WARNINGS” should be used. For example: “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”. If there is more than one warning in the BW title, the word “and” in lower case can separate the warnings. The BW title should be centered.

Comment:

- N/A** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement must be placed immediately beneath the BW title, and should be centered and appear in *italics*.

Comment:

- N/A** 15. The BW must be limited in length to 20 lines. (This includes white space but does not include the BW title and the statement “*See full prescribing information for complete boxed warning.*”)

Comment:

Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the FPI.

Comment:

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 8/2015.”

Comment:

- N/A** 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

Comment:

Dosage Forms and Strengths in Highlights

- YES** 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

Comment:

Contraindications in Highlights

- YES** 20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word “None.”

Comment:

Selected Requirements of Prescribing Information

Adverse Reactions in Highlights

- YES** 21. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**”

Comment:

Patient Counseling Information Statement in Highlights

- YES** 22. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION**

If a product **has (or will have)** FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**
- **See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**

Comment:

Revision Date in Highlights

- YES** 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 8/2015**”).

Comment:

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix for a sample tool illustrating Table of Contents format.

- YES** 24. The TOC should be in a two-column format.
Comment:
- YES** 25. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS.**” This heading should be in all UPPER CASE letters and **bolded**.
Comment:
- N/A** 26. The same title for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment:
- YES** 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- YES** 28. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)].
Comment:
- YES** 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment:
- YES** 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading “**FULL PRESCRIBING INFORMATION: CONTENTS***” must be followed by an asterisk and the following statement must appear at the end of the TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”
Comment:

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 31. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. (Section and subsection headings should be in UPPER CASE and title case, respectively.) If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use "Labor and Delivery")
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use "Nursing Mothers")
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- YES** 32. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[see *Warnings and Precautions (5.2)*].”

Comment:

Selected Requirements of Prescribing Information

- N/A** 33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 34. The following heading “**FULL PRESCRIBING INFORMATION**” must be **bolded**, must appear at the beginning of the FPI, and should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- N/A** 35. All text in the BW should be **bolded**.

Comment:

- N/A** 36. The BW must have a title in UPPER CASE, following the word “**WARNING**” and other words to identify the subject of the warning. (Even if there is more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used.) For example: “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”. If there is more than one warning in the BW title, the word “and” in lower case can separate the warnings.

Comment:

CONTRAINDICATIONS Section in the FPI

- YES** 37. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- YES** 38. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment:

- N/A** 39. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

Selected Requirements of Prescribing Information

PATIENT COUNSELING INFORMATION Section in the FPI

- N/A** 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:
- Advise the patient to read the FDA-approved patient labeling (Patient Information).
 - Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
 - Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
 - Advise the patient to read the FDA-approved patient labeling (Medication Guide).
 - Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Comment:

- N/A** 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) must not be included as a subsection under Section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BEATRICE A KALLUNGAL
03/07/2016

PATRICIA N GARVEY
03/09/2016

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 208114 BLA#	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: <input type="checkbox"/> New Indication (SE1) <input type="checkbox"/> New Dosing Regimen (SE2) <input type="checkbox"/> New Route Of Administration (SE3) <input type="checkbox"/> Comparative Efficacy Claim (SE4) <input type="checkbox"/> New Patient Population (SE5) <input type="checkbox"/> Rx To OTC Switch (SE6) <input type="checkbox"/> Accelerated Approval Confirmatory Study (SE7) <input type="checkbox"/> Labeling Change With Clinical Data (SE8) <input type="checkbox"/> Manufacturing Change With Clinical Data (SE9) <input type="checkbox"/> Animal Rule Confirmatory Study (SE10)
Proprietary Name: Defitelio Established/Proper Name: Defibrotide Dosage Form: Defibrotide Solution for infusion Strengths: 200 mg/2.5mL		
Applicant: Gentium S.p.A. (a Jazz Pharmaceuticals company) Agent for Applicant (if applicable):		
Date of Application: July 30, 2015 Date of Receipt: July 31, 2015 Date clock started after UN:		
PDUFA/BsUFA Goal Date: March 31, 2016		Action Goal Date (if different):
Filing Date: September 29, 2015		Date of Filing Meeting: September 15, 2015
Chemical Classification (original NDAs only) : <input checked="" type="checkbox"/> Type 1- New Molecular Entity (NME); NME and New Combination <input type="checkbox"/> Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination <input type="checkbox"/> Type 3- New Dosage Form; New Dosage Form and New Combination <input type="checkbox"/> Type 4- New Combination <input type="checkbox"/> Type 5- New Formulation or New Manufacturer <input type="checkbox"/> Type 7- Drug Already Marketed without Approved NDA <input type="checkbox"/> Type 8- Partial Rx to OTC Switch		
Proposed indication(s)/Proposed change(s): Treatment of severe hepatic veno-occlusive disease following hematopoietic stem cell transplant (HSCT)		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499		

Type of BLA	<input type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)
If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team	
Review Classification:	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority
The application will be a priority review if:	<input type="checkbox"/> Pediatric WR <input type="checkbox"/> QIDP <input type="checkbox"/> Tropical Disease Priority Review Voucher <input checked="" type="checkbox"/> Pediatric Rare Disease Priority Review Voucher
<ul style="list-style-type: none"> • <i>A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)</i> • <i>The product is a Qualified Infectious Disease Product (QIDP)</i> • <i>A Tropical Disease Priority Review Voucher was submitted</i> • <i>A Pediatric Rare Disease Priority Review Voucher was submitted</i> 	
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)
If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults	

<input checked="" type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> <input checked="" type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies (FDCA Section 505B) <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
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Collaborative Review Division (if OTC product):

List referenced IND Number(s): **IND 062118; IND 052668**

Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA/BsUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are the established/proper and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<i>to the supporting IND(s) if not already entered into tracking system.</i>				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If yes, explain in comment column.			X	
If affected by AIP, has OC been notified of the submission? If yes, date notified:	<input type="checkbox"/>	<input type="checkbox"/>	X	
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>	Payment for this application (<i>check daily email from UserFeeAR@fda.hhs.gov</i>): <input type="checkbox"/> Paid <input checked="" type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>	Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<u>User Fee Bundling Policy</u> <i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i> http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf	Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i> <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A			

505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment																
Is the application a 505(b)(2) NDA? (Check the 356h form, cover letter, and annotated labeling). If yes, answer the bulleted questions below:	<input type="checkbox"/>	<input type="checkbox"/>	X																	
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	<input type="checkbox"/>	<input type="checkbox"/>	X																	
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].	<input type="checkbox"/>	<input type="checkbox"/>	X																	
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]? <i>If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.</i>	<input type="checkbox"/>	<input type="checkbox"/>	X																	
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? <i>Check the Electronic Orange Book at:</i> http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm If yes, please list below:	<input type="checkbox"/>	<input type="checkbox"/>	X																	
<table border="1"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i>																				
Exclusivity	YES	NO	NA	Comment																
Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at:</i> http://www.accessdata.fda.gov/scripts/opdlisting/ood/index.cfm	<input type="checkbox"/>	<input checked="" type="checkbox"/>																		
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>																	
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>																	

If yes, # years requested:				
<i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>				
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>				
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager</i>				
<i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>				

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)			
	<input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission , which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission , does it follow the eCTD guidance? ¹ If not , explain (e.g., waiver granted).	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Index: Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

(NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including: <input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only) If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? If yes, BLA #	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? <i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? <i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i> <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<p><i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i></p> <p><i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i></p>				
Debarment Certification	YES	NO	NA	Comment
<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting²</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		Orphan Designation

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829.htm>

Version: 7/10/2015

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<i>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>				
If the application triggers PREA , is there an agreed Initial Pediatric Study Plan (iPSP)?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Orphan Designation
<i>If no, may be an RTF issue - contact DPMH for advice.</i>				
If required by the agreed iPSP , are the pediatric studies outlined in the agreed iPSP completed and included in the application?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If no, may be an RTF issue - contact DPMH for advice.</i>				
BPCA:				
Is this submission a complete response to a pediatric Written Request?	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>				
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>				
REMS	YES	NO	NA	Comment
Is a REMS submitted?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>				
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If no, request applicant to submit SPL before the filing date.</i>				
Is the PI submitted in PLR format? ⁴	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837.htm>

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	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
For applications submitted on or after June 30, 2015: Is the PI submitted in PLLR format? ⁵	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Even though the subsections of PLLR are included in the USPI, 8.2 (Lactation) does not include 'Risk Summary' which is a required heading.
Has a review of the available pregnancy and lactation data been included?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR/PLLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If no, request in 74-day letter.</i>				
All labeling/packaging sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s):	<input type="checkbox"/>	<input checked="" type="checkbox"/>		No End-of-Phase 2 meeting was held
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): 12/11/2013; 8/21/2014	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s):	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: October 14, 2015

BACKGROUND: Defibrotide is proposed for the treatment of hepatic veno-occlusive disease (VOD), also known as sinusoidal obstruction syndrome (SOS), (b) (4) following hematopoietic stem-cell transplantation (HSCT).

Gentium S.p.A., a Jazz Pharmaceuticals company, submitted a New Drug Application (NDA 208114) for defibrotide with a proposed indication for the treatment of (b) (4) hepatic veno-occlusive disease following hematopoietic stem cell transplant (HSCT).

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Beatrice Kallungal	Y
	CPMS/TL:	Theresa Carioti	
Cross-Discipline Team Leader (CDTL)	R. Angelo De Claro		Y
Division Director/Deputy	Edvardas Kaminskas		Y
Office Director/Deputy	N/A		
Clinical	Reviewer:	Tanya Wroblewski / Donna Przepiorka	Y
	TL:	R. Angelo De Claro	Y
Social Scientist Review (for OTC products)	Reviewer:	N/A	
	TL:	N/A	
OTC Labeling Review (for OTC products)	Reviewer:	N/A	
	TL:	N/A	
Clinical Microbiology (for antimicrobial products)	Reviewer:	N/A	
	TL:	N/A	
Clinical Pharmacology	Reviewer:	Guoxiang (George) Shen	Y
	TL:	Bahru Habtemariam	Y
• Genomics	Reviewer:	N/A	
• Pharmacometrics	Reviewer:	Jee Eun	Y
	TL:	Nitin Mehrotra	Y
Biostatistics	Reviewer:	Xin (Cindy) Gao	Y
	TL:	Yuan-Li Shen	Y

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Brenda Gehrke	Y
	TL:	Christopher Sheth	Y
Statistics (carcinogenicity)	Reviewer:	N/A	
	TL:	N/A	
Product Quality (CMC) Review Team:	ATL:	Janice Brown	Y
	RBPM:	Rabiya Laiq	N
• Drug Substance	Reviewer:	Joseph Leginus	N
• Drug Product	Reviewer:	Nina Ni	N
• Process	Reviewer:	Youmin Wang	Y
• Microbiology	Reviewer:	Jessica Cole	N
	TL	Stephen Langille	Y
• Facility	Reviewer:	Robert Wittorf	N
• Biopharmaceutics	Reviewer:	Gerlie Gieser	N
• Immunogenicity	Reviewer:	N/A	
• Labeling (BLAs only)	Reviewer:	N/A	
• Other (e.g., Branch Chiefs, EA Reviewer)	N/A		
OMP/OMPI/DMPP (Patient labeling: MG, PPI, IFU)	Reviewer:	N/A	
	TL:	N/A	
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labels)	Reviewer:	N/A	
	TL:	N/A	
OSE/DMEPA (proprietary name, carton/container labels)	Reviewer:	Ebony Ayers	Y
	TL:	N/A	
OSE/DRISK (REMS)	Reviewer:	Naomi Redd	Y
	TL:	N/A	
OC/OSI/DSC/PMSB (REMS)	Reviewer:	Anthony Orenca	N
	TL:	Janice Pohlman	N
OSE – Division of Pharmacovigilance	Reviewer	Michael Kieffer	Y
	TL	N/A	
OBP – Viral Control and Product Potency Assay	Reviewer		
	TL	Howard Anderson	Y

Bioresearch Monitoring (OSI)	Reviewer:	N/A	
	TL:	N/A	
Controlled Substance Staff (CSS)	Reviewer:	N/A	
	TL:	N/A	

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505 b)(2) filing issues: <ul style="list-style-type: none"> ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain: The Product Quality review team sent an information request to submit an English translation of the executed batch records for the Defibrotide drug substance and Defibrotide drug product 80 mg/mL</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> No comments

<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA, include the reason. For example:</i></p> <ul style="list-style-type: none"> ○ <i>this drug/biologic is not the first in its class</i> ○ <i>the clinical study design was acceptable</i> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> • If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CONTROLLED SUBSTANCE STAFF</p> <ul style="list-style-type: none"> • Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>New Molecular Entity (NDAs only)</u></p> <ul style="list-style-type: none"> Is the product an NME? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>Comments:</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> Establishment(s) ready for inspection? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>CMC Labeling Review (BLAs only)</u></p> <p>Comments:</p>	<input type="checkbox"/> Review issues for 74-day letter
<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> • Were there agreements made at the application’s pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days? 	<input type="checkbox"/> N/A <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? 	
<ul style="list-style-type: none"> • Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Richard Pazdur, MD	
Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): November 10, 2015	
21st Century Review Milestones (see attached) (listing review milestones in this document is optional):	
Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter. <input type="checkbox"/> Review issues have been identified for the 74-day letter. <u>Review Classification:</u> <input type="checkbox"/> Standard Review <input checked="" type="checkbox"/> Priority Review
ACTION ITEMS	
<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
<input type="checkbox"/>	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input checked="" type="checkbox"/>	If priority review, notify applicant in writing by day 60 (see CST for choices)
<input type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input checked="" type="checkbox"/>	Update the PDUFA V DARRTS page (for applications in the Program)
<input type="checkbox"/>	Other

Annual review of template by OND ADRAAs completed: September 2014

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BEATRICE A KALLUNGAL
03/03/2016

MARA B MILLER
03/03/2016

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

CLINICAL INSPECTION SUMMARY

DATE: February 10, 2016

TO: Beatrice Kallungal, Regulatory Project Manager
Tanya Wroblewski, Medical Officer
Donna Przepiorka, M.D., Ph.D., Medical Officer
R. Angelo de Claro, M.D. Cross Discipline Team Leader
Division of Hematology Products (DHP)

FROM: Anthony Orencia, M.D., F.A.C.P.
Medical Officer, GCP Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

THROUGH: Janice Pohlman, M.D., M.P.H.
Team Leader, GCP Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

Kassa Ayalew, M.D., M.P.H.
Branch Chief, GCP Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 208114

APPLICANT: Jazz Pharmaceuticals, Inc.

DRUG: defibrotide

NME: Yes

THERAPEUTIC CLASSIFICATION/REVIEW: Priority Review

INDICATIONS: hepatic veno-occlusive disease

CONSULTATION REQUEST DATE (signed): September 25, 2015

INSPECTION SUMMARY GOAL DATE (original): January 15, 2016

INSPECTION SUMMARY GOAL DATE (revised): February 12, 2016

DIVISION ACTION GOAL DATE: April 11, 2016

PDUFA DATE: June 29, 2016

I. BACKGROUND:

Patients with hepatic veno-occlusive disease, with case fatality in over 80% of patients, may have hepato-renal syndrome with sodium avidity, portal hypertension, and multi-organ failure. Antithrombotic and thrombolytic agents, such as tissue plasminogen activator with or without concurrent heparin, have been tried as therapeutic agents for veno-occlusive disease.

Defibrotide is an oligonucleotide extracted from porcine intestinal mucosa by controlled depolymerization. Defibrotide has anti-thrombotic, anti-ischemic, anti-inflammatory, anti-adhesive and thrombolytic properties without significant systemic anti-coagulant effects. Defibrotide potentially increases, in part, levels of endogenous prostaglandins, stimulates expression of thrombomodulin in human vascular endothelial cells, modulates platelet activity and stimulates fibrinolysis.

A single adequate clinical trial was submitted in support of NDA 208114. Three U.S. study sites were requested to be inspected. The sites enrolled large numbers of patients for the defibrotide treatment arm.

Study 2005-01

Study 2005-01 was an open label, historical control, multi-center study at 35 sites. Data for the historical control group were collected retrospectively from patient charts and transcribed onto case record forms (CRFs) for entry into the database. Originally, 80 treated patients and 80 historical controls were planned for the study. The assembled cohort comprised a total of 102 patients in the treatment group and 32 patients in the final historical control group, narrowed down during the Medical Review Committee (MRC) selection process from over 6000 records to 32 medical charts for review. CDER DHP confirmed that only the 102 treatment group patients' charts will be available for inspection.

The primary study objective, in part, was to demonstrate the efficacy and safety (toxicity) of 25 mg/kg/day of defibrotide in patients with severe veno-occlusive disease (VOD).

Primary study efficacy endpoint was survival rate 100 days (“D+100 survival”) post stem cell transplant (SCT) in patients with severe VOD treated with defibrotide at a dose of 25 mg/kg/day.

II. RESULTS:

Name of CI Location	Study Site/Protocol 2005-01/Number of Subjects Enrolled (n)	Inspection Date	Classification*
Paul Richardson, MD Dana-Farber Cancer Institute 44 Binney Street Boston, MA 02215	Site #01 Subjects= 13 (treatment group)	November 6-12, 2015	Preliminary: NAI
Angela Smith MD, MS University of Minnesota Medical Center 500 Harvard Street Minneapolis, MN 55455	Site #11 Subjects= 11 (treatment group)	October 13-28, 2015	Preliminary: VAI
Nancy Kernan, MD Memorial Sloan-Kettering Cancer Center 1275 York Ave New York, NY 10065	Site #08 Subjects= 8 (treatment group)	October 28-November 4, 2015	Preliminary: NAI
Jazz Pharmaceuticals 3180 Porter Drive Palo Alto, CA 94304	Sponsor of Study Protocol 2005-01	January 14-27, 2016	Preliminary: VAI

***Key to Classifications**

NAI = No deviation from regulations. Data acceptable.

VAI-No Response Requested = Deviations(s) from regulations. Data acceptable.

OAI = Significant deviations from regulations. Data unreliable/critical findings may affect data integrity.

Preliminary=The Establishment Inspection Report (EIR) has not been received, findings are based on preliminary communication with the field at the Office of Regulatory Affairs (ORA), or final review of the EIR is pending. Once a final letter is issued by CDER to the inspected entity and the case file is closed, the preliminary designation is converted to a final regulatory classification.

CLINICAL STUDY SITE INVESTIGATOR

1. Paul Richardson, M.D.

Boston, MA 02215

a. What was inspected:

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

b. General observations/commentary:

The inspection was conducted from November 6 thru 12, 2015. A total of 14 subjects were screened and 13 subjects enrolled in the study. Seven study subjects completed the study. An audit of all 14 subjects' records was conducted.

Source documents for all enrolled subjects were reviewed and compared to case report forms and NDA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practice. A Form FDA 483 (List of Inspectional Observations) was not issued at the end of the inspection.

c. Assessment of data integrity:

The study appears to have been conducted adequately, and the data generated by this site appear acceptable and may be used in support of this specific indication.

2. Angela Smith, M.D., M.S.

Minneapolis, MN

a. What was inspected:

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

b. General observations/commentary:

The inspection was conducted from October 13 to 28, 2015. A total of 133 patients were screened and 11 subjects enrolled. Five subjects completed the study (minimum of 21 days of treatment). An audit of all 11 subjects' records was conducted.

Source documents for those enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. There were no limitations during conduct of the clinical site inspection.

A Form FDA 483 (Inspectional Observations) was issued at the end of the inspection principally for not conducting the clinical investigation according to the investigational plan. For example:

- (1) SAEs were reported late or not in a timely manner, instead of the 24 hour study protocol requirement after the clinical investigator became aware of the adverse event. Examples:

- (a) Subject #1 had respiratory failure and pulmonary hemorrhage [November 16-20, 2006 episode] but the SAE was reported to the sponsor on February 5, 2007. A separate pulmonary alveolar hemorrhage [September 3-7, 2006 episode] was recorded, but the SAE was reported to the sponsor on November 20, 2006.
- (b) Subject #3 had pulmonary hemorrhage [March 23-24, 2007 episode], but the SAE was reported to the sponsor on July 12, 2013. Subject #3 had cardiac arrest episodes on April 16 and also on April 28, 2007, but the SAE was reported to the sponsor on July 12, 2013.
- (c) Subject #8 experienced hypotension on November 2, 2007, but the SAE was reported to the sponsor on August 5, 2008. Subject #8 also developed multi-organ failure from October 6 to November 2, 2007, but the SAE was reported on June 6, 2008.
- (d) Subject #9 developed pulmonary alveolar hemorrhage and myocardial ischemia [October 6-12, 2007 episode], but the SAE was reported to the sponsor on August 29, 2008.

OSI reviewer comment:

The SAE examples noted above were reported late or there was a delay in the reporting process by the clinical study site to the sponsor. These SAEs were eventually reported to the Agency.

- (2) Incorrect drug dosing calculations were performed for these patients.
 - (a) Subject #01 was administered an extra cumulative 100 mg of the study drug. [45 mg/dose administered for 20 doses before dose adjusted to appropriate 40 mg/dose based on baseline weight]
 - (b) Subject #05 was administered an extra cumulative 400 mg of the study drug. [correct dose of 230 mg/dose for 40 doses, but dose increased to 250 mg/dose for 20 doses]
 - (c) Subject #08 was administered an extra cumulative 4,056 mg of the study drug. [dose of 576 mg/dose rather than 550 mg/dose for 156 doses]
 - (d) Subject #11 was administered an extra cumulative 490 mg of the study drug. [correctly dosed with 460 mg/dose except for 7 doses of 530 mg/dose]

OSI reviewer comment:

The study drug product was to be administered at a dose of 6.25 mg/kg every 6 hours (25 mg/kg/day) calculated on the baseline weight. At this site, personnel including nurse practitioners, residents, fellows, and physician assistants without documentation of training on the protocol were writing orders for administration of study drug. The magnitude of difference in the doses administered (i.e. slight increase in doses administered) would not be expected to have a significant impact on efficacy or safety of the product. The dosing error that occurred in Subject #08 occurred for the entire course of treatment because the subject's dose

was based on a current floor weight, rather than baseline weight and was an isolated error in dosing. Subject #08 died due to progressive veno-occlusive disease and multi-organ failure.

Protocol deviations were reported to the NDA for Subjects 05, 08, and 11. The dosing errors described above were discussed with DHP, who agreed with the assessment that dosing errors were not significant in overall determination of efficacy of subjects. Additionally, DHP commented that technically the question doesn't apply to the determination of safety analyses for this NDA submission, since the determination of safety was based on the actual dose administered rather than the planned dose.

In the clinical site's response to the Form FDA Form 483, (b) (4) stated that during the study enrollment period in 2006 and 2007, pharmacy orders were completed on a paper-based system, which has now graduated into the 2012 University's Electronic Medical Record BEACON electronic system, which has a robust internal safety feature for all bone marrow transplant and oncology protocol treatment template orders. Additionally, as part of the corrective action, physicians on the Delegation of Authority logs and clinical investigators as part of the Form FDA 1572 would be part of a stringent pharmacy tracking and monitoring system.

- (3) Deviations from protocol were not reported to the IRB as required.
 - (a) Administration of a prohibited medication (antithrombin III) while the subject (11-D-07) was still receiving the study drug.
 - (b) Subject 11-D-08 concerning incorrect dosing was not submitted to the IRB. This subject received over 4,200 mg more of the study drug than should have been administered.
 - (4) Various personnel not trained on the study protocol were allowed to perform study related tasks, such as order, hold and discontinue the study drug and perform the Informed Consenting process.

OSI reviewer comment:

In the clinical site's response to the Form FDA 483, (b) (4) are currently working together to create a policy consistent with FDA and NCI CTEP regulations and policies which limits who may write and approve orders for drugs and biologics under IND. Steps have been taken to ensure that any individuals writing such orders are trained on the specific study and included on the FDA Form 1572.

As noted above, (b) (4) responded adequately to the Form FDA 483 issued on November 16, 2015.

c. Assessment of data integrity:

Although the above observations were regulatory violations, the magnitude of the incorrect doses was small and did not impact efficacy analyses. This was confirmed in discussions with DHP. Subject #08's death was attributed to progressive veno-occlusive disease and not drug toxicity. The regulatory violations described above are unlikely to significantly have an impact on the reliability of data submitted by this clinical site, and data submitted by this site appear acceptable in support of this specific indication.

3. Nancy Kernan, M.D.
New York, NY

a. What was inspected:

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

b. General observations/commentary:

The inspection was conducted from October 28 to November 4, 2015. A total of eight subjects were screened and enrolled. Two subjects completed the study. An audit of the eight enrolled subjects' records was conducted.

Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (Inspectional Observations) was not issued at the end of the inspection.

c. Assessment of data integrity:

The study appears to have been conducted adequately, and the data generated by this site appear acceptable and may be used in support of this specific indication.

SPONSOR

4. Jazz Pharmaceuticals
Palo Alto, CA

a. What was inspected:

The inspection was conducted from January 14 – 27, 2016. The inspection evaluated the following: documents related to study monitoring visits and correspondence, Institutional Review Board (IRB) approvals, completed Form FDA 1572s, monitoring reports, drug accountability, and training of staff and site monitors.

b. General observations/commentary:

Following submission of the NDA to FDA and assignments were made for clinical site and sponsor inspections, OSI received a complaint from an anonymous source in transitioning from original paper CRFs (utilized by the initial CRO) to electronic CRFs (provided and utilized by a subsequent CRO) that multiple formats of the eCRFs were sent to the CRO assuming responsibility for the eCRFs, with some data-cleaning changes made to described as self-evident changes (i.e. change in laboratory units, dosing instructions, and adverse events). Concerns were also raised about changes in the statistical analysis plan so that analyses were changed to fit observed, available data.

OSI reviewer comment:

Inspection of source documents at three clinical sites did not find significant discrepancies between source and NDA data listings.

In regards to changes in the statistical analysis plan, the site acknowledged that changes were made in response to FDA recommendations. The ORA investigator was told by the Director of Regulatory Affairs for the sponsor that the migration of data had not caused problems in data analysis; however the statistical analysis did utilize a “window method” to fill in any data gaps. The ORA investigator was not able to substantiate with available evidence that regulatory violations had occurred. The observations were discussed with DHP.

Monitoring deficiencies, in terms of initiating interim monitoring visits within a timely manner, were identified during the inspection.

A Form FDA 483 was issued at the end of the sponsor inspection. Specifically, the sponsor monitoring activities for the clinical conduct of Study 2005-01 from 2006 until 2010 did not detect that some sites had lapsed IRB approvals. Inspectional review of ten sites for continuing IRB review found that five sites had lapsed approvals prior to the site being closed. One of the sites (Site #38 Nationwide Children's Hospital) had an actively enrolled subject during the time that IRB approval had lapsed.

OSI reviewer comment:

The sponsor should have initiated interim monitoring visits within a timely manner and obtained timely IRB approvals for all the sites. Based on OSI's review, there is no evidence that subjects experienced any harms. The above regulatory deficiency was shared with DHP.

c. Assessment of data integrity:

Notwithstanding the above regulatory deficiency that was not critical, data submitted by this sponsor appear acceptable in support of the requested indication.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

A single clinical study was submitted in support of the applicant's NDA. Three domestic clinical study sites (Dr. Richardson, Dr. Smith, and Dr. Kernan) were selected for audit. Sponsor (Jazz Pharmaceuticals) was also inspected.

The preliminary classification for Dr. Richardson and Dr. Kernan is No Action Indicated (NAI). The preliminary classification for Dr. Smith and Jazz Pharmaceuticals is Voluntary Action Indicated (VAI). Although regulatory violations were noted at the Dr. Smith and the sponsor site, the findings appear to be addressed in the NDA submission and unlikely to significantly impact overall assessment of efficacy for this study.

Note: The inspectional observations, for these principal clinical investigators and sponsor, are based on preliminary communications with the ORA field investigator. A clinical inspection summary addendum will be generated if conclusions on the current inspection report change significantly, upon receipt and review of the Establishment Inspection Report (EIR). The CDER OSI classification of inspection is finalized when written correspondence is issued to the inspected entity.

{See appended electronic signature page}

Anthony Orenca, M.D.
Medical Officer
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Janice Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANTHONY J ORENCIA
02/10/2016

JANICE K POHLMAN
02/10/2016

KASSA AYALEW
02/11/2016

**Interdisciplinary Review Team for QT Studies Consultation:
Thorough QT Study Review**

NDA	208114
Generic Name	Defibrotide
Sponsor	Gentium SpA
Indication	Treatment of (b) (4) hepatic veno-occlusive disease in hematopoietic stem cell recipients
Dosage Form	IV infusion
Drug Class	Anti-thrombotic and thrombolytic
Therapeutic Dosing Regimen	6.25 mg/kg IV
Duration of Therapeutic Use	Acute
Maximum Tolerated Dose	15 mg/kg IV
Submission Number and Date	003 and 1/13/2016
Review Division	DHP

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

No significant QTc prolongation effect of defibrotide intravenous solution (6.25 mg/kg and 15 mg/kg) was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean differences between defibrotide (6.25 mg/kg and 15 mg/kg) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the 2-sided 90% CI for $\Delta\Delta\text{QTcI}$ moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 2, indicating that assay sensitivity was established.

In this randomized, placebo- and positive-controlled, 4-period crossover study, 52 healthy subjects received single IV infusions over 2 h of 6.25 mg/kg (therapeutic dose) and 15 mg/kg (supratherapeutic dose) defibrotide, placebo and a single oral dose of moxifloxacin 400 mg. Overall summary of findings is presented in Table 1.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Defibrotide IV Solution (6.5 mg/kg and 15 mg/kg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (hour)	$\Delta\Delta\text{QTcI}$ (ms)	90% CI (ms)
Defibrotide 6.5 mg/kg	3.5	1.1	(-1.3, 3.5)
Defibrotide 15 mg/kg	3.5	3.5	(1.1, 5.9)
*Moxifloxacin 400 mg	2.25	15.6	(13.4, 17.9)

* Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 time points is 12.5 ms (see Table 6).

The supratherapeutic dose (15 mg/kg) produces mean C_{max} values of 3.5-fold the mean C_{max} for the therapeutic dose (6.25 mg) in this TQT study. These concentrations are above those for the predicted worst case scenario (2.7-fold in hepatic VOD patients) and show that at these concentrations there are no detectable prolongations of the QT-interval.

2 PROPOSED LABEL

The following is the sponsor’s proposed labeling language related to QT.

12.2 Pharmacodynamics

Cardiac Electrophysiology

(b) (4)

QT-IRT’s proposed labeling language is a suggestion only. We defer final labeling decisions to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

(b) (4)

3 BACKGROUND

3.1 PRODUCT INFORMATION

Defibrotide is the sodium salt of a polydisperse mixture of predominantly single-stranded (ss) polydeoxyribonucleotides derived from porcine intestinal tissue and having a mean weighted molecular weight (MW) of 13-20 kDa, and a potency of about 27-39 biological units per mg (based on a proprietary assay).

Defibrotide has a complex mechanism of action showing endothelial protective properties, with pro-fibrinolytic, antithrombotic, anti-ischemic, anti-inflammatory, antiadhesive activities, but no significant systemic anti-coagulant effect. It appears to protect endothelial cell injury from chemotherapy-induced apoptosis, without enhancing systemic bleeding and protects sinusoidal endothelium without compromising the antitumor effects of cytotoxic therapy. Preclinical studies demonstrate that defibrotide has profibrinolytic activity and prevents fibrin deposition with selective activity in small vessels.

3.2 MARKET APPROVAL STATUS

Defibrotide is not approved for marketing in any country.

3.3 PRECLINICAL INFORMATION

See Appendix 5.5.

3.4 PREVIOUS CLINICAL EXPERIENCE

See Appendix 5.5.

3.5 CLINICAL PHARMACOLOGY

Appendix 5.5 summarizes the key features of defibrotide's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under IND 62118. The sponsor submitted the study report R09-1425 for the study drug, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

A Double-Blind Randomized Crossover Trial to Define the ECG Effects of Defibrotide Using a Clinical and a Supratherapeutic Dose Compared to Placebo and Moxifloxacin (a Positive Control) in Healthy Men and Women: a Thorough ECG Trial

4.2.2 Protocol Number

R09-1425

4.2.3 Study Dates

Date of First Enrollment: 09 May 2010

Date of Last Completed: 07 June 2010

4.2.4 Objectives

The primary objective of this study was to evaluate the effects of therapeutic (6.25 mg/kg) and suprathreshold (15 mg/kg) doses of defibrotide on QTc prolongation. The secondary objective, a comparison of QTc effect between moxifloxacin (400 mg) and placebo, was included in order to demonstrate assay sensitivity, as required by regulatory guidance.

4.2.5 Study Description

4.2.5.1 Design

This was a single-center, randomized, placebo-and positive-controlled, 4-period crossover thorough QT study. The total duration of the study, screening through study exit, was approximately 8 weeks with at least a 3-day washout period between doses. At study check-in, the subjects reported to the clinical site at least 21 hours prior to Day 1 dosing and were required to stay for 24 hours after dosing of each period.

4.2.5.2 Controls

The Sponsor used both placebo and positive (moxifloxacin) controls.

4.2.5.3 Blinding

Moxifloxacin was not blinded.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

Subjects received each of the following four study products once, in accordance with a randomization schedule, over the course of the study:

- Treatment A (therapeutic defibrotide dose): single IV dose of defibrotide 6.25 mg/kg (administered over 2 hours)
- Treatment B (suprathreshold defibrotide dose): single IV dose of defibrotide 15 mg/kg (administered over 2 hours)
- Treatment C (placebo dose): single IV dose of defibrotide placebo (5% dextrose in water for injection administered over 2 hours)
- Treatment D (moxifloxacin dose): single oral dose of moxifloxacin 400 mg tablet

4.2.6.2 Sponsor's Justification for Doses

The therapeutic dose of defibrotide to be used in this study is 6.25 mg/kg given as a single dose over a 2 hour infusion. The 15 mg/kg dose, which represents one of the highest doses previously administered in clinical trials, was chosen as the suprathreshold dose that is anticipated to be safe in healthy volunteers.

Reviewer's Comment: C_{max} (60.96 ug/mL) following administration of the 15 mg/kg defibrotide suprathapeutic dose in the thorough QT study were 3.5-fold that with 6.25 mg/kg, the intended clinical dose. At the clinical dose of 6.25 mg/kg, C_{max} in hepatic VOD patients was (48.8 ug/mL), which was covered by the supra-therapeutic dose tested in the TQT study.

4.2.6.3 Instructions with Regard to Meals

Reviewer's Comment: Defibrotide is administered by IV infusion. Food is not expected to affect defibrotide exposure significantly.

4.2.6.4 ECG and PK Assessments

Blood samples for the pharmacokinetic (PK) assessment were obtained from all subjects on Day 1 within 90 minutes prior to dose administration and at 1, 2 (immediately prior to the end of infusion), 2.083, 2.25, 2.5, 2.75, 3, 3.5, 4, 6, 12, 18, 23 hours after dosing. When a subject is doses with an IV treatment, the 2.083, 2.25, and 2.5 hour blood draws will be collected in relation to the actual time of the end of the infusion (i.e., blood draws will be collected at 0.083, 0.25, and 0.5 hours after the actual end of infusion).

All endpoint 12-lead ECGs will be downloaded as four ECGs from the flash card at each of the following nominal time points on Day 1: 45, 30, 15 minutes prior to dosing and 1, 2 (immediately prior to the end of infusion), 2.25 2.5, 2.75, 3, 3.5, 4, 6, 12, 18, and 23 hours after dosing.

Reviewer's Comment: The ECG/PK sampling time points are adequate to cover the peak concentration of defibrotide and potential delayed effect up to 23 hours post-dose.

4.2.6.5 Baseline

Sponsor used the average QTc prior to each dose at -45 min., -30 min., and -15 min as baselines.

4.2.7 ECG Collection

Intensive 12-Lead Holter monitoring will be used to obtain digital ECGs. Standard 12-Lead ECGs will be obtained while subjects are recumbent.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

Fifty-two (52) subjects were enrolled in the study and all subjects were healthy adults and 52 subjects completed the clinical portion of the study in its entirety.

4.2.8.1.1 Primary Analysis

The primary endpoint was time-matched baseline-adjusted mean differences between defibrotide (6.25 mg/kg and 15 mg/kg) and placebo in Δ QTcI. The sponsor used a mixed effect model and the results are presented in Table 2. The model included sequence, period, treatment, time, treatment by time interaction, and gender as fixed effects; subject as a random effect; and the predose baseline QTcI as covariate. The sponsor concluded

that defibrotide has no QTcI prolongation effect, as the upper bounds of the 2-sided 90% CIs for the mean differences between therapeutic or suprathreshold doses of defibrotide and placebo were below 10 ms.

Table 2: Sponsor’s $\Delta\Delta$ QTcI Analyses for Defibrotide 6.25 mg/kg , Defibrotide 15 mg/kg and Moxifloxacin 400 mg

Time	Defibrotide 6.25 mg/kg N=52			Defibrotide 15 mg/kg N=52			Moxifloxacin 400 mg N=52		
	Estimate [1]	Lower Bound [2]	Upper Bound [2]	Estimate [1]	Lower Bound [2]	Upper Bound [2]	Estimate [1]	Lower Bound [2]	Upper Bound [2]
1 Hr	-0.7	-3.1	1.7	-0.2	-2.6	2.2	8.5	4.8	12.1
2 Hr	0.0	-2.4	2.4	-0.4	-2.9	2.0	11.7	8.0	15.3
2.25 Hr	0.2	-2.2	2.6	0.8	-1.7	3.2	15.7	12.0	19.3
2.5 Hr	0.2	-2.2	2.6	0.9	-1.6	3.3	15.1	11.5	18.7
2.75 Hr	0.3	-2.1	2.7	1.3	-1.1	3.7	13.7	10.0	17.3
3 Hr	-0.2	-2.6	2.2	1.6	-0.8	4.0	11.4	7.8	15.1
3.5 Hr	0.9	-1.5	3.3	3.4	0.9	5.8	9.3	5.6	12.9
4 Hr	0.1	-2.3	2.5	0.2	-2.2	2.7	8.5	4.9	12.1
6 Hr	-1.5	-3.9	0.9	-0.3	-2.7	2.1	5.3	1.6	8.9
12 Hr	1.3	-1.1	3.7	-0.2	-2.6	2.3	7.0	3.4	10.7
18 Hr	-1.5	-3.9	0.9	-1.9	-4.3	0.5	3.1	-0.5	6.8
23 Hr	-0.2	-2.6	2.2	-0.8	-3.2	1.7	5.4	1.8	9.1
Time Ave	-0.1	-1.5	1.3	0.3	-1.1	1.7	9.5	8.1	11.0

[1] Mixed Effects General Linear Model (placebo-adjusted, baseline-corrected) is fit for QTc Individual (ms) change and includes terms for: treatment, gender, time, time by treatment interaction, baseline value and gender by baseline interaction of QTc Individual (ms).

[2] Lower/Upper Bound = lower/upper two-sided 90% (one-sided 95%) model-based confidence limit. p-values for gender effects are: Gender Main Effect = 0.0182, Gender-Baseline Interaction = 0.0239

Source: Table 14.2.9.17

Reviewer’s Comments: We will provide our independent analysis results in Section 5.2. Our results are similar to the sponsor’s results of QTcI.

4.2.8.1.2 Assay Sensitivity

The sponsor used the same mixed model to analyze the $\Delta\Delta$ QTcI effect for moxifloxacin. The results are presented in Table 2. The lower bounds of the 2-sided 90% CI for the mean differences between moxifloxacin and placebo were greater than or equal to 5 ms met at 4 of the 6 time points, therefore establishing assay sensitivity.

Reviewer’s Comments: We will provide our independent analysis results in Section 5.2. Our results are similar to the sponsor’s results of QTcI.

4.2.8.1.3 Categorical Analysis

Categorical analysis was used to summarize in the categories of QTc \leq 450 ms, between

450 ms and 480 ms, between 480 ms and 500 ms, and >500 ms, and changes from baseline QTc \leq 30 ms, between 30 and 60 ms, and >60 ms. No subject's absolute QTc >480 ms and Δ QTc >60 ms.

4.2.8.2 Safety Analysis

Thirteen (13) subjects experienced a total of 33 AEs over the course of the study. All AEs were mild in intensity. No deaths, no SAEs were reported.

Overall, the most common AEs reported were vessel puncture site haematoma, headache, infusion site extravasation, nausea, feeling hot, back pain, and diarrhoea. Vessel puncture site haematoma, infusion site extravasation, and back pain occurred on at least one occasion in 2 subjects (3.8%) and generally were considered by the investigator to be not related to the study treatment. Nausea and feeling hot occurred on at least one occasion in 2 subjects (3.8%) and was considered by the investigator to be possibly related to study treatment. Diarrhoea occurred in 2 subjects (3.8%) on at least one occasion and was considered to be possibly related to study treatment on two occasions, and not related to study treatment on one occasion. Headache occurred on one occasion in 3 subjects (5.8%) and was considered by the investigator to be possibly related to study treatment on two occasions, and not related to study treatment on one occasion.

4.2.8.3 Clinical Pharmacology

4.2.8.3.1 Pharmacokinetic Analysis

The PK results are presented in the following table and figure. C_{max} following administration of the 15 mg/kg defibrotide suprathapeutic dose in the thorough QT study were 3.5-fold that with 6.25 mg /kg given by IV infusion over 2 h, the intended clinical dose.

Table 11.4.7-1 Arithmetic Mean (\pm SD) Defibrotide Pharmacokinetic Parameters for All Subjects

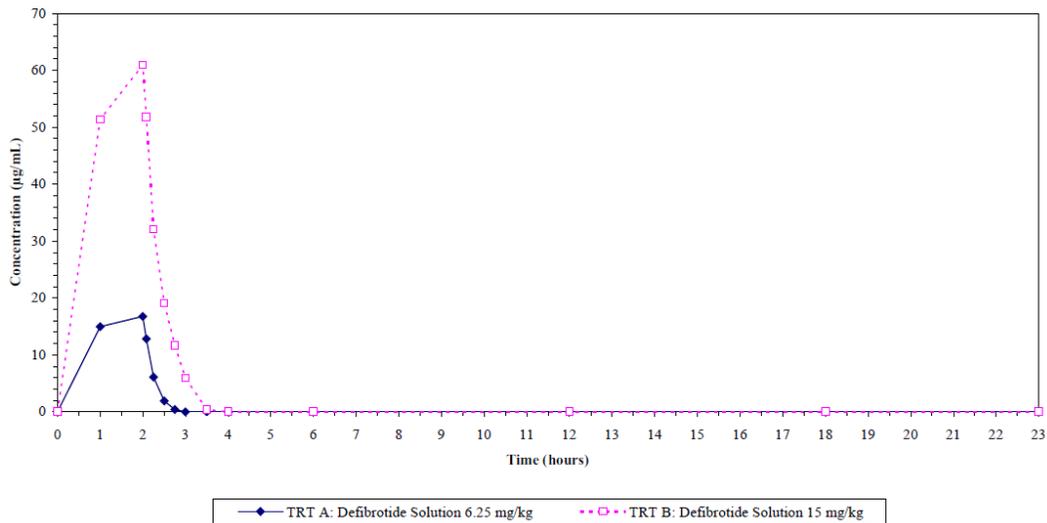
PK Parameter	Treatment A (Therapeutic Dose) N=52**		Treatment B (Supratherapeutic Dose) N=52**	
	Mean (\pm SD)	N	Mean (\pm SD)	N
AUC _{0-t} (μ g·hr/mL)	26.86 (\pm 8.53)	51	105.22 (\pm 22.60)	52
AUC _{0-inf} (μ g·hr/mL)	48.14 (\pm 6.49)	12	113.59 (\pm 23.54)	50
C _{max} (μ g/mL)	17.27 (\pm 3.83)	51	60.96 (\pm 11.83)	52
T _{max} * (hr)	2.00 (1.00 – 2.00)	51	2.00 (2.00 – 2.08)	52
Kel (1/hr)	1.2484 (\pm 0.66)	12	1.7533 (\pm 0.62)	50
T _{1/2} (hr)	0.71 (\pm 0.35)	12	0.45 (\pm 0.17)	50
Vd (mL)	9934.07 (\pm 3806.87)	12	6188.45 (\pm 2262.34)	50
CL (L/hr)	10.35 (\pm 1.77)	12	9.76 (\pm 1.65)	50

* Median and range are reported.

** Total number of subjects in the evaluable population

Source: R09-1425 study report, page 56.

Figure 11.4.7-1 Mean Defibrotide Plasma Concentration versus Time Profile: Linear Scale (N=52)

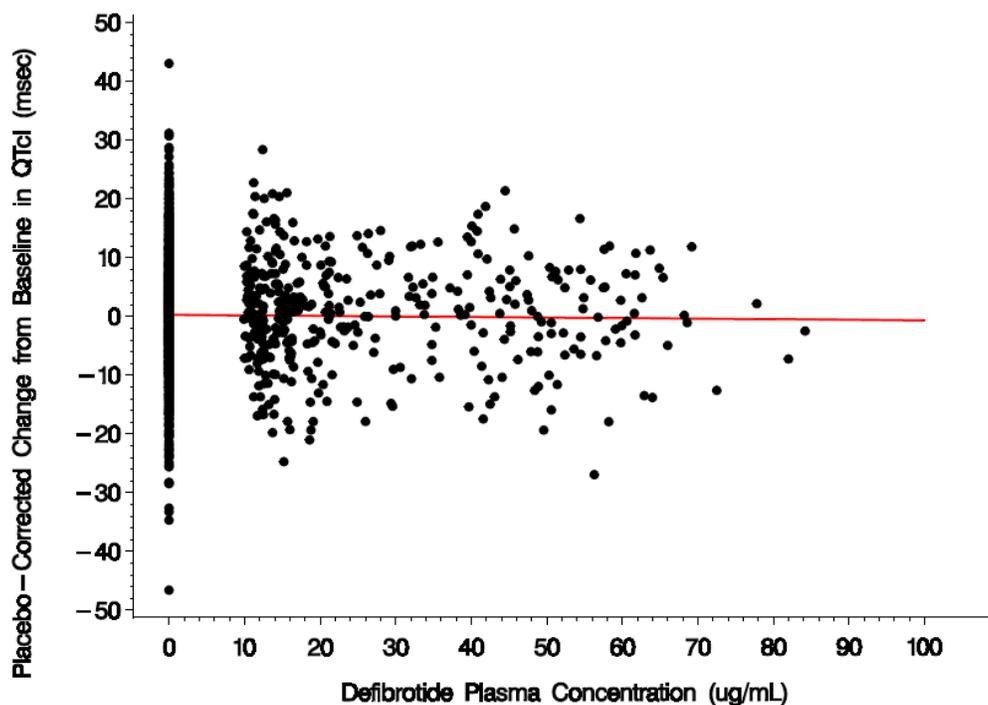


Source: R09-1425 study report, page 55.

4.2.8.3.2 Exposure-Response Analysis

Concentration-QTc relationship for defibrotide was investigated with linear mixed effect modeling and no significant relationship was observed (see the following figure).

Figure 12.5.2.3-1 QTcI Placebo – Corrected Change from Baseline versus Defibr Plasma Concentration (PK – PD Analysis)



Source: R09-1425 study report, page 75.

Reviewer's Analysis: A plot of $\Delta\Delta QTcI$ vs. defibr concentrations is presented in Figure 3, with no evident relationship.

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

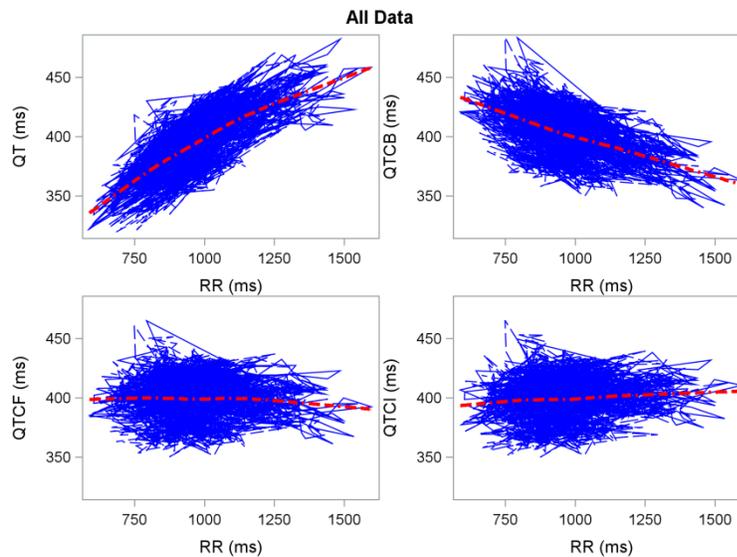
We used the criterion of Mean Sum of Squared Slopes (MSSS) from individual regressions of QTc versus RR. The smaller this value is, the better the correction. Based on the results listed in Table 3, it appears that QTcF and QTcI are similar better than QTcB. To be consistent with the sponsor's analyses, QTcI was used in the primary statistical analysis. We also perform a secondary analysis using QTcF and obtain similar results.

Table 3: Average of Sum of Squared Slopes for Different QT-RR Correction Methods

Treatment Group	Correction Method					
	QTcI		QTcB		QTcF	
	N	MSSS	N	MSSS	N	MSSS
Defibrotide 15 mg/kg	52	0.0012	52	0.0048	52	0.0010
Defibrotide 6.25 mg/kg	52	0.0014	52	0.0063	52	0.0012
Moxifloxacin 400 mg	52	0.0021	52	0.0041	52	0.0015
Placebo	51	0.0013	51	0.0054	51	0.0016
All	52	0.0011	52	0.0049	52	0.0007

The relationship between different correction methods and RR is presented in Figure 1.

Figure 1: QT, QTcB, QTcF, and QTcI vs. RR (Each Subject's Data Points are Connected with a Line)



5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for Defibrotide

The statistical reviewer used mixed model to analyze the Δ QTcI effect. The model includes treatment as a fixed effect and baseline value as a covariate. The analysis results are listed in Table 4. The largest upper bounds of the 2-sided 90% CI for the mean differences between defibrotide 6.25 mg/kg and placebo, and between defibrotide 15 mg/kg are 3.5 ms and 5.9 ms, respectively.. The results of QTcF and QTcI are similar

that the upper bounds of the treatment groups are lower than 10 ms of the regulatory concern as described in ICH E14 guidelines.

Table 4: Analysis Results of Δ QTcI and $\Delta\Delta$ QTcI for Defibrotide 6.25 mg/kg and Defibrotide 15 mg/kg

Time (h)	Treatment Group								
	Placebo	Defibrotide 15 mg/kg				Defibrotide 6.25 mg/kg			
	Δ QTcI	Δ QTcI		$\Delta\Delta$ QTcI		Δ QTcI		$\Delta\Delta$ QTcI	
	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
1	-4.6	52	-4.8	-0.2	(-2.5, 2.0)	52	-5.3	-0.7	(-2.9, 1.5)
2	-6.1	52	-6.6	-0.5	(-2.7, 1.7)	52	-6.1	0.0	(-2.2, 2.2)
2.25	-8.3	52	-7.5	0.7	(-1.5, 3.0)	52	-8.0	0.3	(-2.0, 2.5)
2.5	-8.2	52	-7.4	0.9	(-1.2, 2.9)	52	-8.0	0.3	(-1.8, 2.3)
2.75	-7.6	52	-6.3	1.3	(-1.0, 3.6)	52	-7.3	0.3	(-2.0, 2.6)
3	-5.6	52	-4.0	1.6	(-0.9, 4.0)	51	-5.7	-0.2	(-2.6, 2.3)
3.5	-3.1	52	0.4	3.5	(1.1, 5.9)	52	-2.0	1.1	(-1.3, 3.5)
4	-2.2	52	-2.0	0.2	(-2.1, 2.6)	52	-2.0	0.2	(-2.2, 2.5)
6	-8.4	51	-8.6	-0.2	(-3.0, 2.6)	52	-9.8	-1.4	(-4.2, 1.3)
12	-10.3	51	-10.4	-0.1	(-2.6, 2.4)	51	-8.8	1.4	(-1.1, 4.0)
18	6.7	51	4.8	-1.9	(-4.9, 1.1)	52	5.2	-1.5	(-4.5, 1.5)
23	-1.9	51	-2.5	-0.7	(-3.8, 2.4)	52	-2.0	-0.1	(-3.2, 3.0)

Table 5: Analysis Results of Δ QTcF and $\Delta\Delta$ QTcF for Defibrotide 6.25 mg/kg, Defibrotide 15 mg/kg and Moxifloxacin 400 mg

	Treatment Group												
	Placebo	Defibrotide 15 mg/kg				Defibrotide 6.25 mg/kg				Moxifloxacin 400 mg			
	Δ QTcF	Δ QTcF	$\Delta\Delta$ QTcF			Δ QTcF	$\Delta\Delta$ QTcF			Δ QTcF	$\Delta\Delta$ QTcF		
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
1	-4.4	52	-4.9	-0.5	(-2.8, 1.7)	52	-5.3	-0.9	(-3.2, 1.4)	52	3.8	8.1	(5.9, 10.4)
2	-6.2	52	-6.5	-0.3	(-2.6, 1.9)	52	-5.9	0.3	(-1.9, 2.6)	52	5.4	11.6	(9.4, 13.9)
2.25	-8.4	52	-7.6	0.9	(-1.5, 3.2)	52	-7.7	0.7	(-1.7, 3.0)	52	7.2	15.6	(13.3, 18.0)
2.5	-8.4	52	-7.3	1.1	(-1.0, 3.2)	52	-7.4	1.0	(-1.1, 3.0)	52	6.8	15.2	(13.1, 17.3)
2.75	-7.9	52	-6.2	1.7	(-0.7, 4.1)	52	-7.2	0.7	(-1.7, 3.1)	52	5.9	13.8	(11.4, 16.2)
3	-5.3	52	-4.4	0.9	(-1.6, 3.5)	51	-5.4	-0.1	(-2.7, 2.4)	52	5.7	11.0	(8.4, 13.5)
3.5	-3.1	52	0.0	3.1	(0.7, 5.5)	52	-1.9	1.2	(-1.2, 3.6)	52	6.2	9.3	(6.9, 11.7)
4	-2.0	52	-1.8	0.2	(-2.2, 2.6)	52	-1.9	0.1	(-2.4, 2.5)	52	6.0	8.0	(5.6, 10.5)
6	-6.9	51	-7.2	-0.3	(-3.3, 2.7)	52	-7.5	-0.6	(-3.6, 2.4)	51	-1.8	5.1	(2.1, 8.1)
12	-9.4	51	-9.1	0.2	(-2.5, 2.9)	51	-7.6	1.8	(-0.9, 4.5)	51	-2.5	6.9	(4.1, 9.6)
18	6.3	51	4.8	-1.5	(-4.5, 1.6)	52	4.7	-1.5	(-4.6, 1.6)	52	8.8	2.6	(-0.5, 5.7)
23	-1.7	51	-2.6	-0.9	(-4.1, 2.4)	52	-1.1	0.6	(-2.6, 3.8)	52	3.9	5.6	(2.4, 8.8)

5.2.1.2 Assay Sensitivity Analysis

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data. The results are presented in Table 6. The largest unadjusted 90% lower confidence interval is 13.4 ms. By considering Bonferroni multiple endpoint adjustment, the largest lower confidence interval is 12.5 ms, which indicates that an at least 5 ms QTcI effect due to moxifloxacin can be detected from the study.

Table 6: Analysis Results of Δ QTcI and $\Delta\Delta$ QTcI for Moxifloxacin 400 mg

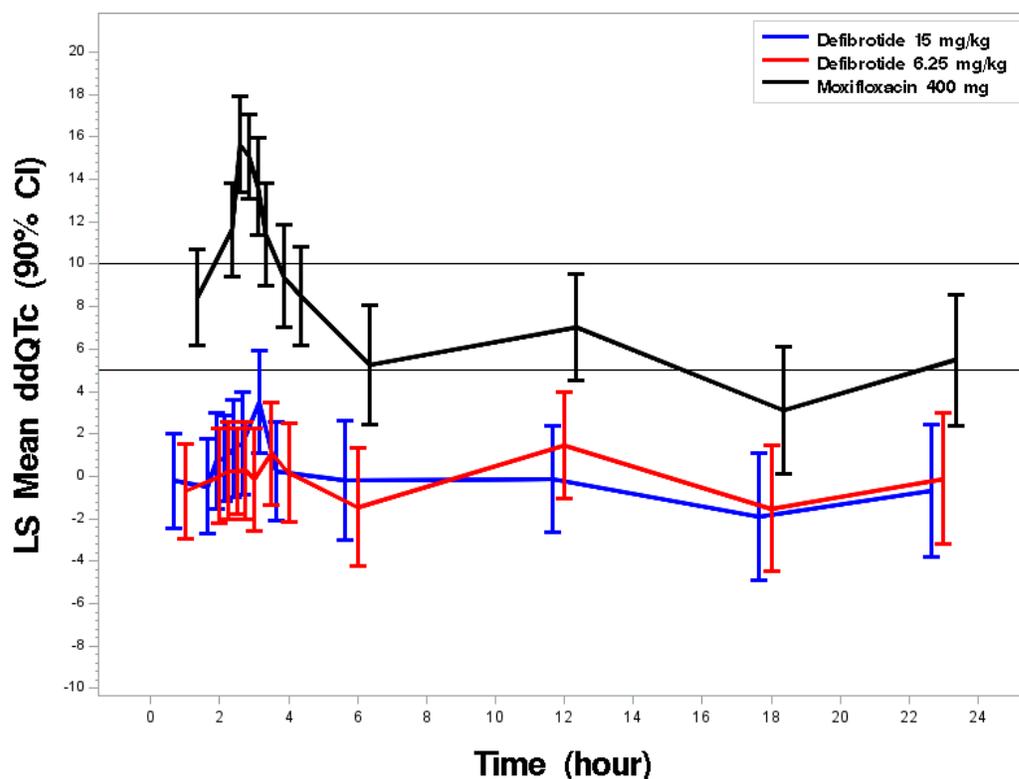
	Treatment Group					
	Placebo	Moxifloxacin 400 mg				
	Δ QTcI	Δ QTcI		$\Delta\Delta$ QTcI		
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	Adj. 90% CI*
1	-4.6	52	3.8	8.4	(6.2, 10.7)	(5.4, 11.5)
2	-6.1	52	5.5	11.6	(9.4, 13.8)	(8.6, 14.7)
2.25	-8.3	52	7.4	15.6	(13.4, 17.9)	(12.5, 18.7)
2.5	-8.2	52	6.9	15.1	(13.1, 17.1)	(12.3, 17.8)
2.75	-7.6	52	6.0	13.7	(11.4, 15.9)	(10.5, 16.8)
3	-5.6	52	5.9	11.4	(9.0, 13.8)	(8.1, 14.7)
3.5	-3.1	52	6.3	9.4	(7.0, 11.8)	(6.1, 12.7)
4	-2.2	52	6.3	8.5	(6.2, 10.8)	(5.3, 11.7)
6	-8.4	51	-3.1	5.3	(2.5, 8.1)	(1.4, 9.1)
12	-10.3	51	-3.3	7.0	(4.5, 9.5)	(3.6, 10.4)
18	6.7	52	9.8	3.1	(0.1, 6.1)	(-1.0, 7.2)
23	-1.9	52	3.6	5.5	(2.4, 8.6)	(1.3, 9.7)

* Bonferroni method was applied for multiple endpoint adjustment of 4 time points (significant at the 0.025 level).

5.2.1.3 Graph of $\Delta\Delta$ QTcI Over Time

The following figure displays the time profile of $\Delta\Delta$ QTcI for different treatment groups.

Figure 2: Mean and 90% CI $\Delta\Delta$ QTcI Time Course



5.2.1.4 Categorical Analysis

Table 7 list the number of subjects as well as the number of observations whose QTcI values are ≤ 450 ms, between 450 ms and 480 ms, between 480 ms and 500 ms, and >500 ms. No subject's QTcF is above 480 ms.

Table 7: Categorical Analysis for QTcI

Treatment Group	Total N	Value ≤ 450 ms	450 $\text{ms} < \text{Value} \leq 480$ ms	480 $\text{ms} < \text{Value} \leq 500$ ms	Value > 500
Defibrotide 15 mg/kg	52	52 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Defibrotide 6.25 mg/kg	52	51 (98.1%)	1 (1.9%)	0 (0.0%)	0 (0.0%)
Moxifloxacin 400 mg	52	52 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Placebo	51	51 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 8 lists the number of subjects changes from baseline QTc ≤ 30 ms, between 30 and 60 ms, between 60 ms and 90, and >90 ms. No subject's change from baseline is above 60 ms.

Table 8: Categorical Analysis of Δ QTcI

Treatment Group	Total N	Value\leq30 ms	30 ms<Value\leq60 ms	60 ms<Value\leq90 ms	Value>90 ms
Defibrotide 15 mg/kg	52	51 (98.1%)	1 (1.9%)	0 (0.0%)	0 (0.0%)
Defibrotide 6.25 mg/kg	52	52 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Moxifloxacin 400 mg	52	52 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Placebo	50	49 (98.0%)	1 (2.0%)	0 (0.0%)	0 (0.0%)

5.2.2 HR Analysis

The statistical reviewer used mixed model to analyze the Δ HR effect. The model includes treatment as a fixed effect and baseline value as a covariate. The analysis results are listed in Table 9. The largest upper bounds of the 2-sided 90% CI for the mean differences between defibrotide 6.25 mg/kg and placebo, and between defibrotide 15 mg/kg and placebo are 5.2 bpm and 4.8 bpm, respectively. The categorical analysis of HR is given in Table 10. One subject who experienced HR interval greater than 100 bpm is in defibrotide 15-mg/kg group.

Table 9: Analysis Results of Δ HR and $\Delta\Delta$ HR for Defibrotide 6.25 mg/kg, Defibrotide 15 mg/kg and Moxifloxacin 400 mg

		Treatment Group											
		Defibrotide 15 mg/kg				Defibrotide 6.25 mg/kg				Moxifloxacin 400 mg			
		Δ HR		$\Delta\Delta$ HR		Δ HR		$\Delta\Delta$ HR		Δ HR		$\Delta\Delta$ HR	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
1	1.5	52	-1.0	-2.5	(-3.9, -1.1)	52	0.6	-0.9	(-2.2, 0.5)	52	3.2	1.8	(0.4, 3.1)
2	1.8	52	0.8	-1.0	(-2.6, 0.5)	52	1.5	-0.3	(-1.8, 1.2)	52	3.7	1.9	(0.3, 3.4)
2.25	2.6	52	2.3	-0.3	(-2.0, 1.3)	52	1.7	-0.9	(-2.6, 0.7)	52	3.7	1.0	(-0.6, 2.7)
2.5	1.4	52	2.0	0.6	(-0.9, 2.1)	52	2.4	1.0	(-0.5, 2.5)	52	3.8	2.5	(1.0, 3.9)
2.75	0.7	52	2.3	1.6	(0.0, 3.2)	52	1.0	0.3	(-1.3, 1.8)	52	2.8	2.1	(0.6, 3.7)
3	2.5	52	2.2	-0.3	(-1.9, 1.3)	52	2.3	-0.2	(-1.9, 1.4)	52	4.1	1.6	(-0.0, 3.2)
3.5	1.5	52	2.6	1.0	(-0.7, 2.7)	52	2.8	1.2	(-0.5, 2.9)	52	3.3	1.8	(0.1, 3.4)
4	2.7	52	3.3	0.6	(-0.9, 2.1)	52	2.7	-0.1	(-1.5, 1.4)	52	3.2	0.5	(-1.0, 2.0)
6	12.9	51	12.9	-0.0	(-2.5, 2.4)	52	13.1	0.2	(-2.3, 2.6)	51	13.0	0.1	(-2.3, 2.5)
12	9.3	51	12.1	2.7	(0.7, 4.8)	51	10.1	0.8	(-1.2, 2.8)	51	10.3	0.9	(-1.1, 3.0)
18	-1.9	51	-2.0	-0.1	(-2.1, 1.9)	52	-1.5	0.4	(-1.6, 2.4)	52	-2.1	-0.2	(-2.2, 1.8)
23	2.1	51	3.1	1.0	(-1.4, 3.5)	52	4.8	2.7	(0.2, 5.2)	52	3.9	1.9	(-0.6, 4.3)

Table 10: Categorical Analysis for HR

Treatment Group	Total N	HR \leq 100 bpm	HR $>$ 100 bpm
Defibrotide 15 mg/kg	52	51 (98.1%)	1 (1.9%)
Defibrotide 6.25 mg/kg	52	52 (100%)	0 (0.0%)
Moxifloxacin 400 mg	52	51 (98.1%)	1 (1.9%)
Placebo	51	51 (100%)	0 (0.0%)

5.2.3 PR Analysis

The statistical reviewer used mixed model to analyze the Δ PR effect. The model includes treatment as a fixed effect and baseline value as a covariate. The analysis results are listed in

Table 11. The largest upper bounds of the 2-sided 90% CI for the mean differences between defibrotide 6.25 mg/kg and placebo, and between defibrotide 15 mg/kg and placebo are 4.6 ms and 5.5 ms, respectively. The categorical analysis of PR is given in Table 12. One subject who experienced PR interval greater than 200 ms is in defibrotide 6.5-mg/kg group.

Table 11: Analysis Results of Δ PR and $\Delta\Delta$ PR for Defibrotide 6.25 mg/kg, Defibrotide 15 mg/kg and Moxifloxacin 400 mg

Time (h)	Treatment Group												
	Placebo	Defibrotide 15 mg/kg				Defibrotide 6.25 mg/kg				Moxifloxacin 400 mg			
	Δ PR	Δ PR		$\Delta\Delta$ PR		Δ PR		$\Delta\Delta$ PR		Δ PR		$\Delta\Delta$ PR	
	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
1	1.4	52	1.5	0.1	(-1.9, 2.1)	52	2.4	1.0	(-1.0, 3.0)	52	-1.2	-2.6	(-4.6, -0.6)
2	1.3	52	0.7	-0.5	(-2.5, 1.5)	52	1.7	0.5	(-1.6, 2.5)	52	-1.6	-2.9	(-4.9, -0.8)
2.25	-1.1	52	-0.0	1.1	(-1.0, 3.1)	52	-0.8	0.3	(-1.7, 2.4)	52	-1.8	-0.7	(-2.8, 1.3)
2.5	-2.2	52	-1.4	0.8	(-1.4, 3.0)	52	-1.1	1.1	(-1.1, 3.3)	52	-2.2	0.1	(-2.2, 2.3)
2.75	-2.9	52	-2.6	0.3	(-1.7, 2.4)	52	-2.3	0.7	(-1.4, 2.7)	52	-2.2	0.7	(-1.4, 2.8)
3	-3.5	52	-2.4	1.2	(-0.9, 3.2)	52	-1.9	1.6	(-0.4, 3.7)	52	-2.7	0.9	(-1.2, 2.9)
3.5	-4.1	51	-2.6	1.4	(-0.8, 3.7)	51	-3.5	0.6	(-1.6, 2.8)	52	-3.1	0.9	(-1.3, 3.2)
4	-3.6	52	-3.2	0.4	(-1.8, 2.5)	52	-3.7	-0.1	(-2.2, 2.1)	52	-4.7	-1.2	(-3.3, 1.0)
6	-8.7	51	-8.0	0.7	(-2.1, 3.5)	52	-7.4	1.3	(-1.5, 4.0)	51	-10.1	-1.4	(-4.2, 1.3)
12	-4.2	51	-3.7	0.5	(-2.1, 3.1)	51	-3.1	1.1	(-1.6, 3.7)	51	-4.0	0.2	(-2.4, 2.8)
18	-0.4	51	2.1	2.6	(-0.3, 5.5)	52	1.3	1.7	(-1.1, 4.6)	52	1.6	2.0	(-0.8, 4.9)
23	-3.5	51	-4.0	-0.5	(-2.8, 1.8)	52	-1.8	1.7	(-0.7, 4.0)	52	-3.0	0.5	(-1.8, 2.8)

Table 12: Categorical Analysis for PR

Treatment Group	Total	PR \leq 200 ms	PR $>$ 100 ms
	N		
Defibrotide 15 mg/kg	52	52 (100%)	0 (0.0%)
Defibrotide 6.25 mg/kg	52	51 (98.1%)	1 (1.9%)
Moxifloxacin 400 mg	52	51 (98.1%)	1 (1.9%)
Placebo	51	50 (98.0%)	1 (2.0%)

5.2.4 QRS Analysis

The statistical reviewer used mixed model to analyze the Δ QRS effect. The model includes treatment as a fixed effect and baseline value as a covariate. The analysis results are listed in Table 13. The largest upper bounds of the 2-sided 90% CI for the mean differences between defibrotide 6.25 mg/kg and placebo, and between defibrotide 15 mg/kg and placebo are 1.1 ms and 1.0 ms, respectively. The categorical analysis of QRS is given in Table 14. Two subjects who experienced QRS interval greater than 110 ms are in defibrotide 6.5-mg/kg group.

Table 13: Analysis Results of Δ QRS and $\Delta\Delta$ QRS PR for Defibrotide 6.25 mg/kg, Defibrotide 15 mg/kg and Moxifloxacin 400 mg

Time (h)	Treatment Group												
	Placebo	Defibrotide 15 mg/kg				Defibrotide 6.25 mg/kg				Moxifloxacin 400 mg			
	Δ QRS	Δ QRS		$\Delta\Delta$ QRS		Δ QRS		$\Delta\Delta$ QRS		Δ QRS		$\Delta\Delta$ QRS	
	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
1	0.3	52	0.4	0.1	(-0.6, 0.8)	52	0.7	0.4	(-0.3, 1.1)	52	-0.3	-0.6	(-1.2, 0.1)
2	0.1	52	0.0	-0.1	(-0.8, 0.6)	52	0.5	0.4	(-0.3, 1.1)	52	-0.1	-0.2	(-0.9, 0.5)
2.25	-0.2	52	-0.3	-0.1	(-0.9, 0.6)	52	0.1	0.3	(-0.4, 1.1)	52	-0.2	-0.0	(-0.8, 0.7)
2.5	-0.3	52	-0.1	0.1	(-0.5, 0.8)	52	-0.3	-0.1	(-0.7, 0.6)	52	-1.1	-0.8	(-1.5, -0.1)
2.75	-0.5	52	-0.6	-0.1	(-0.8, 0.7)	52	0.1	0.6	(-0.1, 1.3)	52	-1.0	-0.5	(-1.2, 0.3)
3	-0.8	52	-0.4	0.4	(-0.3, 1.0)	51	-0.4	0.3	(-0.3, 1.0)	52	-0.8	-0.0	(-0.7, 0.7)
3.5	-0.3	52	-0.6	-0.2	(-0.9, 0.5)	52	-0.5	-0.1	(-0.8, 0.6)	52	-0.6	-0.3	(-1.0, 0.4)
4	-0.8	52	-0.7	0.1	(-0.6, 0.9)	52	-0.6	0.2	(-0.5, 1.0)	52	-0.4	0.4	(-0.3, 1.2)
6	-1.1	51	-1.1	-0.0	(-1.0, 1.0)	52	-2.0	-0.9	(-1.9, 0.1)	51	-1.4	-0.4	(-1.4, 0.6)
12	-0.7	51	-2.0	-1.3	(-2.3, -0.3)	51	-1.0	-0.4	(-1.4, 0.6)	51	-0.8	-0.1	(-1.1, 0.9)
18	1.7	51	0.4	-1.4	(-2.4, -0.4)	52	1.2	-0.6	(-1.6, 0.4)	52	0.9	-0.9	(-1.9, 0.1)
23	0.2	51	-0.5	-0.7	(-1.7, 0.4)	52	-0.8	-1.0	(-2.0, 0.1)	52	-0.8	-0.9	(-2.0, 0.1)

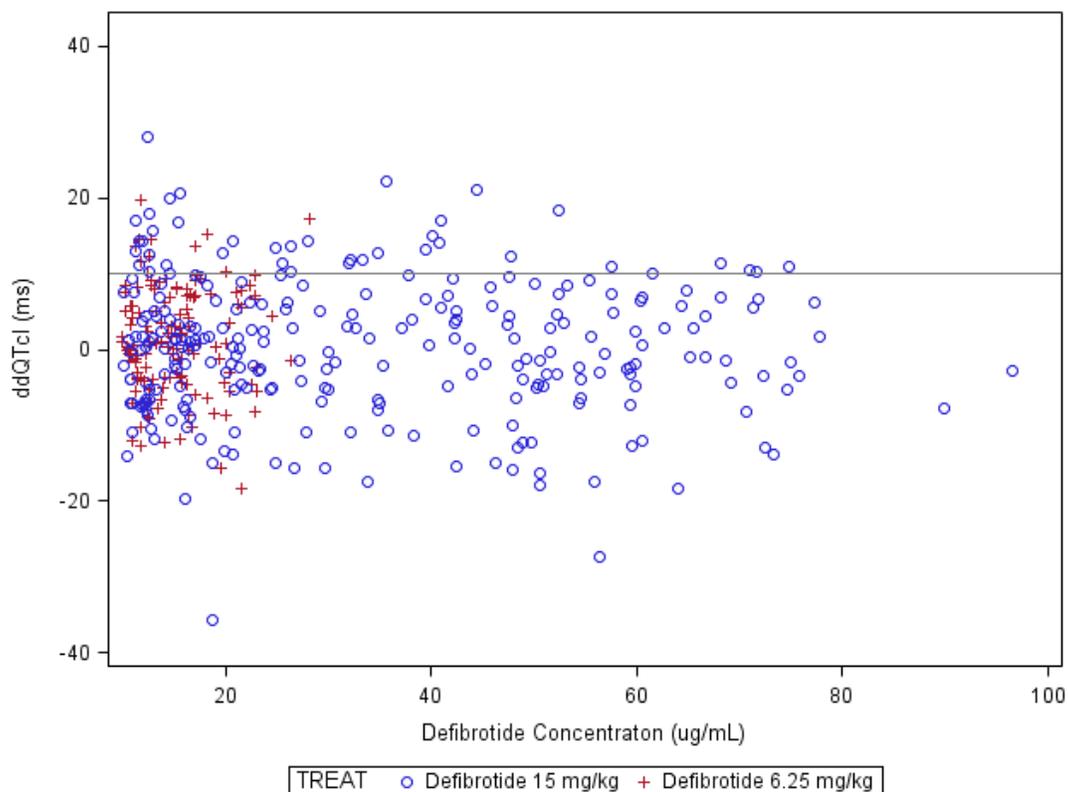
Table 14: Categorical Analysis for QRS

Treatment Group	Total N	QRS \leq 110 ms	QRS $>$ 110 ms
Defibrotide 15 mg/kg	52	52 (100%)	0 (0.0%)
Defibrotide 6.25 mg/kg	52	50 (96.2%)	2 (3.8%)
Moxifloxacin 400 mg	52	51 (98.1%)	1 (1.9%)
Placebo	51	51 (100%)	0 (0.0%)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The relationship between $\Delta\Delta$ QTcI and defibrotide concentrations is visualized in Figure 3 with no evident exposure-response relationship.

Figure 3: Scatter Plot of $\Delta\Delta\text{QTcI}$ vs. Defibrotide Concentration



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E14 guidelines (i.e., syncope, seizure, significant ventricular arrhythmias or sudden cardiac death) occurred in this study.

5.4.2 ECG assessments

Overall ECG acquisition and interpretation in this study appears acceptable.

5.4.3 PR and QRS Interval

There were no clinically relevant effects on PR and QRS intervals.

5.4.4 APPENDIX

5.5 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose and exposure	<p>Include maximum proposed clinical dosing regimen Mean (%CV) C_{max} and AUC at the single maximum proposed clinical dose Mean (%CV) C_{max} and AUC at the steady state with the maximum proposed clinical dosing regimen</p> <p>The sole proposed clinical dosing regimen for defibrotide is 6.25 mg/kg q6h by intravenous infusion over 2 hours (25 mg/kg/day).</p> <p>The observed C_{max} and AUC values after single dose and steady state administration of 6.25 mg/kg to patients with veno-occlusive disease (VOD) in Phase 2 Study 99-118 are presented below.</p> <table border="1" data-bbox="553 642 1357 821"> <thead> <tr> <th rowspan="3">Parameter</th> <th colspan="4">Defibrotide Doses in Phase 2 Study 99-118</th> </tr> <tr> <th colspan="2">Day 2^a (n=5) (6.25 mg/kg, single dose)</th> <th colspan="2">Day 7^b (n=5) (6.25 mg/kg, steady state)</th> </tr> <tr> <th>Mean</th> <th>CV (%)</th> <th>Mean</th> <th>CV (%)</th> </tr> </thead> <tbody> <tr> <td>AUC_{0-t} (µg•h/mL)</td> <td>87.7</td> <td>35.2</td> <td>99.1</td> <td>61.6</td> </tr> <tr> <td>C_{max} (µg/mL)</td> <td>45.8</td> <td>30.4</td> <td>48.8</td> <td>57.4</td> </tr> </tbody> </table> <p>^a Samples drawn after first infusion on Day 2 (first dose at 6.25 mg/kg) ^b Samples drawn after first infusion on Day 7 (steady state at 6.25 mg/kg)</p> <p>Similarly, the observed C_{max} and AUC values after single dose administration of 6.25 mg/kg and 15 mg/kg to healthy subjects in the completed QT Study R09-1425 are presented below.</p> <table border="1" data-bbox="545 1016 1317 1220"> <thead> <tr> <th rowspan="3">Parameter</th> <th colspan="4">Defibrotide Doses in QT Study R09-1425</th> </tr> <tr> <th colspan="2">6.25 mg/kg, single dose (therapeutic dose)</th> <th colspan="2">15 mg/kg, single dose (supratherapeutic dose)</th> </tr> <tr> <th>Mean</th> <th>CV %</th> <th>Mean</th> <th>CV %</th> </tr> </thead> <tbody> <tr> <td>AUC_{0-inf} (µg•h/mL)</td> <td>48.14</td> <td>13.48</td> <td>113.59</td> <td>20.72</td> </tr> <tr> <td>C_{max} (µg/mL)</td> <td>17.27</td> <td>22.15</td> <td>60.96</td> <td>19.41</td> </tr> </tbody> </table>	Parameter	Defibrotide Doses in Phase 2 Study 99-118				Day 2 ^a (n=5) (6.25 mg/kg, single dose)		Day 7 ^b (n=5) (6.25 mg/kg, steady state)		Mean	CV (%)	Mean	CV (%)	AUC _{0-t} (µg•h/mL)	87.7	35.2	99.1	61.6	C _{max} (µg/mL)	45.8	30.4	48.8	57.4	Parameter	Defibrotide Doses in QT Study R09-1425				6.25 mg/kg, single dose (therapeutic dose)		15 mg/kg, single dose (supratherapeutic dose)		Mean	CV %	Mean	CV %	AUC _{0-inf} (µg•h/mL)	48.14	13.48	113.59	20.72	C _{max} (µg/mL)	17.27	22.15	60.96	19.41
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Maximum tolerated dose	<p>Include if studied or NOAEL dose</p> <p>The highest dose studied as a single dose in a company-sponsored trial is 15 mg/kg in QT Study R09-1425.</p> <p>The highest dose studied as a multiple dose is 10 mg/kg q6h in Phase 2 Study 99-118.</p>																																														

Principal adverse events	<p>Include most common adverse events; dose limiting adverse events</p> <p>The overall safety profile of defibrotide is based on 176 adult and pediatric patients (Studies 2005-01 and 99-118) with hepatic veno-occlusive disease (VOD) and renal and/or pulmonary dysfunction following hematopoietic stem cell transplant (HSCT) who received the recommended dose of 25 mg/kg/day administered by intravenous infusion as 6.25 mg/kg/dose every 6 hours.</p> <p>The most common adverse events* (incidence $\geq 10\%$) with defibrotide treatment were hypotension, diarrhea, vomiting, nausea, and epistaxis. The most common serious adverse events* (incidence $\geq 2\%$) were hypotension (11.4%), hemorrhagic events (including pulmonary alveolar hemorrhage [7.4%], gastrointestinal hemorrhage [4.0%], pulmonary hemorrhage [3.4%], and intracranial hemorrhage [2.8%]), sepsis (4.5%), graft versus host disease (4.0%), pneumonia (3.4%), hyperuricemia (2.3%), and thrombotic thrombocytopenic purpura (2.3%).</p> <p>There were 35 (34%) patients with at least 1 adverse event who permanently discontinued treatment in Study 2005-01 (N=102). Adverse reactions leading to permanent discontinuation in Study 2005-01 included pulmonary alveolar hemorrhage in 5 (4.9%) patients; pulmonary hemorrhage, hypotension, catheter site hemorrhage, and multi-organ failure, each in 3 (2.9%) patients; and cerebral hemorrhage and sepsis, each in 2 (2%) patients.</p> <p>*Excluding events of underlying disease: multi-organ failure, veno-occlusive disease, renal failure, respiratory failure, and hypoxia.</p>												
Maximum dose tested	Single Dose	<p>Specify dose</p> <p>The highest dose studied as single dose in a company-sponsored trial is 15 mg/kg in QT Study (R09-1425).</p>											
	Multiple Dose	<p>Specify dosing interval and duration</p> <p>The highest dose studied as a multiple dose is 10 mg/kg q6h in Phase 2 Study (99-118). Defibrotide was administered for a minimum of 14 days, and treatment was to continue until the occurrence of complete response. The median length of treatment was 20.0 days.</p>											
Exposures Achieved at Maximum Tested Dose	Single Dose	<p>Mean (%CV) Cmax and AUC</p> <table border="1" data-bbox="779 1302 1331 1480"> <thead> <tr> <th rowspan="2">Parameter</th> <th colspan="2">Study R09-1425 15 mg/kg, single dose (supratherapeutic dose)</th> </tr> <tr> <th>Mean</th> <th>CV (%)</th> </tr> </thead> <tbody> <tr> <td>AUC_{0-inf} ($\mu\text{g}\cdot\text{h}/\text{mL}$)</td> <td>113.59</td> <td>20.72</td> </tr> <tr> <td>C_{max} ($\mu\text{g}/\text{mL}$)</td> <td>60.96</td> <td>19.41</td> </tr> </tbody> </table>	Parameter	Study R09-1425 15 mg/kg, single dose (supratherapeutic dose)		Mean	CV (%)	AUC _{0-inf} ($\mu\text{g}\cdot\text{h}/\text{mL}$)	113.59	20.72	C _{max} ($\mu\text{g}/\text{mL}$)	60.96	19.41
Parameter	Study R09-1425 15 mg/kg, single dose (supratherapeutic dose)												
	Mean	CV (%)											
AUC _{0-inf} ($\mu\text{g}\cdot\text{h}/\text{mL}$)	113.59	20.72											
C _{max} ($\mu\text{g}/\text{mL}$)	60.96	19.41											
	Multiple Dose	<p>Mean (%CV) Cmax and AUC</p> <table border="1" data-bbox="779 1522 1331 1690"> <thead> <tr> <th rowspan="2">Parameter</th> <th colspan="2">Study 99-118 10 mg/kg q6h, Day 7 at steady state</th> </tr> <tr> <th>Mean</th> <th>CV (%)</th> </tr> </thead> <tbody> <tr> <td>AUC_{0-t} ($\mu\text{g}\cdot\text{h}/\text{mL}$)</td> <td>113.7</td> <td>29.5</td> </tr> <tr> <td>C_{max} ($\mu\text{g}/\text{mL}$)</td> <td>57.6</td> <td>29.5</td> </tr> </tbody> </table>	Parameter	Study 99-118 10 mg/kg q6h, Day 7 at steady state		Mean	CV (%)	AUC _{0-t} ($\mu\text{g}\cdot\text{h}/\text{mL}$)	113.7	29.5	C _{max} ($\mu\text{g}/\text{mL}$)	57.6	29.5
Parameter	Study 99-118 10 mg/kg q6h, Day 7 at steady state												
	Mean	CV (%)											
AUC _{0-t} ($\mu\text{g}\cdot\text{h}/\text{mL}$)	113.7	29.5											
C _{max} ($\mu\text{g}/\text{mL}$)	57.6	29.5											

Range of linear PK	Specify dosing regimen PK is approximately linear over the range of doses studied in the QT study (R09-1425). Over the 2.4-fold increase in dose (6.25 mg/kg over 2 hours to 15 mg/kg over 2 hours), mean C _{max} increased 3.5-fold and AUC increased 2.4-fold.																					
Accumulation at steady state	Mean (%CV); specify dosing regimen No accumulation was observed with the proposed clinical regimen (6.25 mg/kg IV infusion over 2hr, four times a day).																					
Metabolites	Include listing of all metabolites and activity Defibrotide is biotransformed to nucleotides, nucleosides, free 2'-deoxyribose sugar, purine and pyrimidine bases. No active metabolites were identified.																					
Absorption	Absolute/Relative Bioavailability	Mean (%CV) 100% (IV infusion)																				
	T _{max}	<ul style="list-style-type: none"> Median (range) for parent T_{max} occurs at approximately 2 hours (end of infusion). <table border="1"> <thead> <tr> <th rowspan="3">Parameter</th> <th colspan="4">Defibrotide Doses in QT Study R09-1425</th> </tr> <tr> <th colspan="2">6.25 mg/kg, single dose (therapeutic dose)</th> <th colspan="2">15 mg/kg, single dose (supratherapeutic dose)</th> </tr> <tr> <th>Median</th> <th>Range</th> <th>Median</th> <th>Range</th> </tr> </thead> <tbody> <tr> <td>T_{max} (h)</td> <td>2.00</td> <td>1.00-2.00</td> <td>2.00</td> <td>2.00-2.08</td> </tr> </tbody> </table> <ul style="list-style-type: none"> Median (range) for metabolites Not Applicable 			Parameter	Defibrotide Doses in QT Study R09-1425				6.25 mg/kg, single dose (therapeutic dose)		15 mg/kg, single dose (supratherapeutic dose)		Median	Range	Median	Range	T _{max} (h)	2.00	1.00-2.00	2.00	2.00-2.08
Parameter	Defibrotide Doses in QT Study R09-1425																					
	6.25 mg/kg, single dose (therapeutic dose)		15 mg/kg, single dose (supratherapeutic dose)																			
	Median	Range	Median	Range																		
T _{max} (h)	2.00	1.00-2.00	2.00	2.00-2.08																		
Distribution	Vd/F or Vd	Mean (%CV) <table border="1"> <thead> <tr> <th rowspan="3">Parameter</th> <th colspan="4">Defibrotide Doses in QT Study R09-1425</th> </tr> <tr> <th colspan="2">6.25 mg/kg, single dose (therapeutic dose)</th> <th colspan="2">15 mg/kg, single dose (supratherapeutic dose)</th> </tr> <tr> <th>Mean</th> <th>CV%</th> <th>Mean</th> <th>CV%</th> </tr> </thead> <tbody> <tr> <td>Vd (L)</td> <td>9.93</td> <td>38.32</td> <td>6.19</td> <td>36.56</td> </tr> </tbody> </table>			Parameter	Defibrotide Doses in QT Study R09-1425				6.25 mg/kg, single dose (therapeutic dose)		15 mg/kg, single dose (supratherapeutic dose)		Mean	CV%	Mean	CV%	Vd (L)	9.93	38.32	6.19	36.56
	Parameter	Defibrotide Doses in QT Study R09-1425																				
6.25 mg/kg, single dose (therapeutic dose)		15 mg/kg, single dose (supratherapeutic dose)																				
Mean		CV%	Mean	CV%																		
Vd (L)	9.93	38.32	6.19	36.56																		
% bound	Mean (%CV) Defibrotide is highly protein bound to human plasma proteins with mean of 93% and CV% of 1.6. Mean and CV% are based on data from Study 8313003 (In Vitro Plasma Protein Binding and Blood to Plasma Partitioning of Defibrotide in Mouse, Rat, Rabbit, Dog, and Human) across defibrotide concentrations of 5, 10, 50, 200, and 500 µg/mL.																					
Elimination	Route	<ul style="list-style-type: none"> Primary route; percent dose eliminated Metabolism followed by urinary excretion. Other routes 5% to 15% renal excretion as unchanged defibrotide. 																				

	Terminal t _{1/2}	<p>• Mean (%CV) for parent</p> <table border="1"> <thead> <tr> <th rowspan="3">Parameter</th> <th colspan="4">Defibrotide Doses in QT Study R09-1425</th> </tr> <tr> <th colspan="2">6.25 mg/kg, single dose (therapeutic dose)</th> <th colspan="2">15 mg/kg, single dose (supratherapeutic dose)</th> </tr> <tr> <th>Mean</th> <th>CV%</th> <th>Mean</th> <th>CV%</th> </tr> </thead> <tbody> <tr> <td>T_{1/2} (h)</td> <td>0.71</td> <td>49.37</td> <td>0.45</td> <td>38.75</td> </tr> </tbody> </table> <p>• Mean (%CV) for metabolites Not Applicable</p>	Parameter	Defibrotide Doses in QT Study R09-1425				6.25 mg/kg, single dose (therapeutic dose)		15 mg/kg, single dose (supratherapeutic dose)		Mean	CV%	Mean	CV%	T _{1/2} (h)	0.71	49.37	0.45	38.75
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	Mean	CV%	Mean	CV%																
CL (L/h)	10.35	17.05	9.76	16.88																
Intrinsic Factors	Age	<p>Specify mean changes in C_{max} and AUC At a given mg/kg dose, predicted exposure is lower in pediatric VOD patients than in adult VOD patients, and gradually rises to adult values with increasing patient age. Based on population PK analysis, a typical AUC for defibrotide following an intravenous dose of 6.25 mg/kg every 6 hours to a 1-month-old patient would be about 50% of that expected for an adult VOD patient, rising to about 90% of adult values for a 16-year-old patient.</p>																		
	Sex	<p>Specify mean changes in C_{max} and AUC No changes</p>																		
	Race	<p>Specify mean changes in C_{max} and AUC No changes</p>																		
	Hepatic & Renal Impairment	<p>Specify mean changes in C_{max} and AUC Based on the PK study DF VOD-2012-03-PKRen, C_{max} was approximately 35% to 37% higher and AUC was approximately 50% to 60% higher in the renal-impaired end stage disease patients versus healthy matching subjects, following single and multiple administrations of 6.25 mg/kg defibrotide. Based on the Phase 2 study 99-118 in patients with VOD who have hepatic impairment, AUC was approximately 1.8-fold higher and C_{max} approximately 2.7-fold higher in the hepatically impaired patients versus healthy subjects (Study R09-1425), following single administration of 6.25 mg/kg defibrotide.</p>																		

Extrinsic Factors	Drug interactions	<p>Include listing of studied DDI studies with mean changes in C_{max} and AUC No clinical pharmacokinetic drug-drug interaction studies were conducted. Data from in vitro studies using human biomaterial demonstrate that defibrotide does not induce (CYP1A2, CYP2B6, CYP3A4, UGT1A1) or inhibit (CYP1A2, CYP2B6, CYP3A4, CYP2C8, CYP2C9, CYP2C19, CYP2D6, UGT1A1, UGT2B7) the major drug metabolizing enzymes and is not a substrate or inhibitor of the major drug uptake transporters (OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3) or efflux transporters (P-gp and BCRP).</p>																						
	Food Effects	<p>Specify mean changes in C_{max} and AUC and meal type (i.e., high-fat, standard, low-fat) Food effects were not studied due to the route of administration (IV infusion).</p>																						
Expected High Clinical Exposure Scenario	<p>Describe worst case scenario and expected fold-change in C_{max} and AUC. The increase in exposure should be covered by the supra-therapeutic dose. Patients with hepatic VOD and renal and/or pulmonary dysfunction following hematopoietic stem cell transplant (HSCT) (Study 99-118) have lower clearance than either healthy subjects (Study R09-1425) or subjects with renal disease without VOD (Study DF VOD-2012-03-PKRen). At the clinical dose of 6.25 mg/kg, AUC was approximately 1.8-fold higher and C_{max} approximately 2.7-fold higher in VOD patients versus healthy subjects. However, defibrotide exposure in VOD patients at the clinical dose is covered by the exposure in healthy subjects at the supra-therapeutic dose of 15 mg/kg tested in the thorough QT Study R09-1425 (data presented below).</p> <table border="1" data-bbox="568 1155 1339 1360"> <thead> <tr> <th rowspan="2">Parameter</th> <th colspan="2">Study 99-118 Day 7 at steady state at 6.25 mg/kg (therapeutic dose)</th> <th colspan="2">Study R09-1425 single dose at 15 mg/kg (supratherapeutic dose)</th> </tr> <tr> <th>Mean</th> <th>CV (%)</th> <th>Mean</th> <th>CV (%)</th> </tr> </thead> <tbody> <tr> <td>AUC* (µg•h/mL)</td> <td>99.1</td> <td>61.6</td> <td>113.59</td> <td>20.72</td> </tr> <tr> <td>C_{max} (µg/mL)</td> <td>48.8</td> <td>57.4</td> <td>60.96</td> <td>19.41</td> </tr> </tbody> </table> <p>* AUC_{0-t} for Study 99-118 and AUC_{0-inf} for Study R09-1425</p>					Parameter	Study 99-118 Day 7 at steady state at 6.25 mg/kg (therapeutic dose)		Study R09-1425 single dose at 15 mg/kg (supratherapeutic dose)		Mean	CV (%)	Mean	CV (%)	AUC* (µg•h/mL)	99.1	61.6	113.59	20.72	C _{max} (µg/mL)	48.8	57.4	60.96	19.41
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Preclinical Cardiac Safety	<p>Summarize <i>in vitro</i> and <i>in vivo</i> results per S7B guidance. Consistent with ICH S7B guidance, the general non-clinical testing strategy for assessing risk for delayed ventricular repolarization and QT interval prolongation with defibrotide included an in vitro assay and an in vivo assay. Defibrotide (50, 150, or 500 µg/mL) did not reduce human ether-a-go-go related gene (hERG) voltage-gated potassium (K⁺) channel tail current in in vitro patch clamp experiments with human embryonic kidney cells (HEK293), and therefore is not considered a hERG channel blocker (Study 0040-2010). In vivo, defibrotide administration to dogs four times daily via 2-hour IV infusions for 13 consecutive weeks at 0 (vehicle), 60, 300, or 1600 mg/kg/day (Study 1529-002) did not result in any qualitative or quantitative abnormalities of electrocardiographic (ECG) parameters.</p>																							

Clinical Cardiac Safety	<p>Describe total number of clinical trials and number of subjects at different drug exposure levels. Summarize cardiac safety events per ICH E14 guidance (e.g., QT prolongation, syncope, seizures, ventricular arrhythmias, ventricular tachycardia, ventricular fibrillation, flutter, torsade de pointes, or sudden deaths).</p> <p>Overview</p> <p>The overall safety profile of defibrotide is based on 176 adult and pediatric patients (Studies 2005-01 and 99-118) with hepatic VOD and renal and/or pulmonary dysfunction following HSCT who received the recommended dose of 25 mg/kg/day administered by intravenous infusion as 6.25 mg/kg/dose every 6 hours. Study 2005-01 enrolled 102 patients with hepatic VOD and renal and/or pulmonary dysfunction and compared them to 32 historical controls. Study 99-118 was a randomized, two-arm study in patients with hepatic VOD with renal and/or pulmonary dysfunction after HSCT (using doses of 25 and 40 mg/kg/day); there were 74 patients treated with the recommended dose of defibrotide at 25 mg/kg/day. The 176 patients treated at the indicated dose of 25 mg/kg/day included 111 adults and 65 pediatric patients (<16 years old).</p> <p>Data regarding possible cardiac toxicity and arrhythmogenic potential is also available from two studies in healthy volunteers and renal disease patients, Study R09-1425 (thorough QT study) and Study DF VOD-2012-03-PKRen (end stage renal disease PK study).</p> <p>Cardiac adverse events in VOD patients after HSCT</p> <p>Table A below is a summary of treatment-emergent adverse events (TEAEs) from the cardiac system organ class (SOC) reported in $\geq 2\%$ of patients in the total defibrotide group (N=176) from Study 2005-01 and Study 99-118. The incidence of all cardiac disorder events was similar between the two defibrotide dosing groups of 25 mg/kg/day and 40 mg/kg/day (30.7% and 28.0%, respectively) and much less than the incidence in the Historical control group (65.6%). There were more events of supraventricular arrhythmia in the defibrotide 40 mg/kg/day group than in the 25 mg/kg/day group (5 [6.7%] vs 2 [1.1%]). Conclusions regarding the arrhythmogenic potential of defibrotide at the indicated dose of 25 mg/kg/day are difficult to make, given the similar incidences in the 25 mg/kg/day group of both tachycardia- and bradycardia-type events and the significant comorbidities of clinical trial patients with VOD and renal and/or pulmonary dysfunction such as infection/sepsis, coagulopathy, thrombotic thrombocytopenic purpura, disseminated intravascular coagulation, graft versus host disease, acute respiratory distress syndrome and systemic inflammatory reaction.</p>
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Study R09-1425

In this thorough QT study, 52 healthy adult volunteers were randomized according to each treatment sequence and received Treatments A-D in one of 4 treatment periods:

- Treatment A: Defibrotide 6.25 mg/kg (therapeutic dose)
- Treatment B: Defibrotide 15 mg/kg (supratherapeutic dose)
- Treatment C: Placebo (5% DEXTROSE Injection USP)
- Treatment D: AVELOX[®] (moxifloxacin) 400 mg tablet

The results of this ECG trial showed no signal of any effect on heart rate, AV conduction, or cardiac depolarization as measured by the PR and QRS interval durations. There were no new clinically relevant morphological changes. The validity of this trial is demonstrated by the following:

- The moxifloxacin positive control group showed the expected change in QTc duration.
- The placebo group's change from baseline was within 5 ms for QTcI which shows that the spontaneous factors for QTc change were well controlled.

This well conducted and valid (assay sensitivity being reached and placebo group showing control of background QTc variability) thorough ECG trial demonstrated that defibrotide had no effects on heart rate, PR and QRS interval duration or cardiac morphology. The effects on cardiac repolarization by the preponderance of data including a careful pharmacodynamic-pharmacokinetic analysis (using both the therapeutic and supra-therapeutic dose) also show that defibrotide does not affect cardiac repolarization.

The complete [R09-1425 clinical study report](#) (CSR) is available in NDA SN-0002, July 31, 2015, Module 5.3.4.1.

Study DF VOD-2012-03-PKRen

Study DF VOD-2012-03-PKRen was a Phase 1, open-label study conducted in 2 centers to investigate the pharmacokinetics of defibrotide administered to patients with renal impairment.

Twelve adult patients, 6 in each of two cohorts (healthy adults and matched adult severe- to end-stage renal disease patients) were evaluated.

Defibrotide 6.25 mg/kg was safe and well tolerated when administered as a single 2-hour IV infusion before and during hemodialysis to patients with end-stage renal disease and when administered as multiple 2-hour IV infusions to patients with severe to end-stage renal disease not on dialysis and to healthy subjects.

There were no clinically significant laboratory test results, vital sign measurements, physical examination findings, or ECG findings over the course of both studies.

Conclusion

Based on safety data from one Phase 3 pivotal study, one Phase 2 dose-finding study, a renal PK study, and a thorough QT study, there is no evidence to date of any cardiac toxicity or risk of acute cardiac arrhythmia with intravenous defibrotide therapy at the indicated dose in patients with hepatic VOD and renal and/or pulmonary dysfunction after HSCT.

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/s/

MOH JEE NG
02/05/2016

QIANYU DANG
02/05/2016

JIANG LIU
02/05/2016

MICHAEL Y LI
02/07/2016

CHRISTINE E GARNETT
02/08/2016

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: December 14, 2015
Requesting Office or Division: Division of Hematology Products (DHP)
Application Type and Number: NDA 208114
Product Name and Strength: Defitelio (Defibrotide) Injection, 200 mg/2.5 mL (80 mg/mL)
Submission Date: December 7, 2015
Applicant/Sponsor Name: Jazz Pharmaceuticals, Inc.
OSE RCM #: 2015-1785-2
DMEPA Primary Reviewer: Nicole Garrison PharmD, BCPS
DMEPA Team Leader: Yelena Maslov, PharmD

1 PURPOSE OF MEMO

The Division of Hematology Products (DHP) requested that we review the revised container label and carton labeling for Defitelio (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review¹.

2 CONCLUSION

The revised container label and carton labeling for Defitelio is acceptable from a medication error perspective. We have no further recommendations at this time.

¹ Garrison N. Label and Labeling Review Memo for Defitelio (NDA 208114). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 NOV 30. 3 p. OSE RCM No.: 2015-1785-1.

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/s/

NICOLE B GARRISON
12/14/2015

YELENA L MASLOV
12/14/2015

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: November 30, 2015
Requesting Office or Division: Division of Hematology Products (DHP)
Application Type and Number: NDA 208114
Product Name and Strength: Defitelio (Defibrotide) Injection, 200 mg/ 2.5 mL (80 mg/mL)
Submission Date: November 16, 2015
Applicant/Sponsor Name: Jazz Pharmaceuticals, Inc
OSE RCM #: 2015-1785-1
DMEPA Primary Reviewer: Nicole Garrison, PharmD, BCPS
DMEPA Team Leader: Yelena Maslov, PharmD

1 PURPOSE OF MEMO

The Division of Hematology Products (DHP) requested that we review the revised container label and carton labeling for Defitelio (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.¹

2 CONCLUSION

The revised container label and carton labeling for Defitelio need further revisions from a medication error perspective. We identified the following areas of vulnerability to error in the revised container label and carton labeling:

- The statement [REDACTED] ^{(b) (4)} is not an acceptable dosage form².

¹ Garrison N. Label and Labeling Review for Defitelio (NDA 208114). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 OCT 27. 9 p. OSE RCM No.: 2015-1785.

² USP General Chapter <1> Injections

- The warning statement “Must be diluted before intravenous infusion” is not prominent in its current location on the back panel of the carton labeling.

3 RECOMMENDATIONS FOR JAZZ PHARMACEUTICALS, INC

We recommend the following be implemented prior to approval of this NDA:

- A. Container label
 - 1. Revise the statement [REDACTED] ^{(b) (4)} to read “For intravenous infusion only” as solution for intravenous injection is not an acceptable dosage form³.
- B. Carton labeling
 - 1. See A.1 and revise the carton labeling accordingly.
 - 2. To minimize the risk of the product being administered without dilution, we recommend moving the warning statement “Must be diluted before intravenous infusion” to the principal display panel if space permits.

1 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

³ USP General Chapter <1> Injections

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/s/

NICOLE B GARRISON
11/30/2015

YELENA L MASLOV
11/30/2015

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review: October 27, 2015
Requesting Office or Division: Division of Hematology Products (DHP)
Application Type and Number: NDA 208114
Product Name and Strength: Defitelio (Defibrotide) Injection, 200 mg/2.5 mL (80 mg/mL)
Product Type: Single ingredient Product
Rx or OTC: Rx
Applicant/Sponsor Name: Jazz Pharmaceuticals, Inc.
Submission Date: July 31, 2015
OSE RCM #: 2015-1785
DMEPA Primary Reviewer: Nicole Garrison, PharmD, BCPS
DMEPA Team Leader: Yelena Maslov, PharmD

1 REASON FOR REVIEW

This review evaluates the proposed labels and labeling for Defitelio injection, 200 mg/2.5 mL (NDA 208114) for areas of vulnerability that could lead to medication errors. The Division of Hematology Products requested this review as part of their evaluation to the 505(b) (1) submission for Defitelio injection.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C- N/A
ISMP Newsletters	D- N/A
FDA Adverse Event Reporting System (FAERS)*	E- N/A
Other	F- N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Jazz Pharmaceuticals, Inc. submitted a 505 (b) (1) NDA to obtain marketing approval of Defitelio injection. If approved, this will be only therapy in the United States for the treatment of hepatic veno-occlusive disease. Defitelio is supplied as a solution for injection. The proposed product will be supplied as single (b) (4) vials that should be administered every 6 hours.

We reviewed the proposed prescribing information, container labels, and carton labeling and identified the following areas of vulnerability to errors:

- Readability of the Dosage and Administration in the prescribing information, container labels, and carton labeling.

DMEPA concludes that the proposed label and labeling can be improved to increase the readability and prominence of important information on the label to promote safe use of the product. The recommendations can be found in Section 4.

4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed label and labeling can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information

1. Revise all instances of the “TRADENAME” to the conditionally acceptable proprietary name DEFITELIO.
2. In section 2.1 (Recommended Dose)
 - a. To improve clarity of dosing information, we recommend the dose of Defitelio should be revised to “6.25 mg/kg/dose every 6 hours”.
3. In section 2.2 (Treatment Modification)
 - a. Dangerous abbreviations, symbols, and dose designations that are included on the Institute of Safe Medication Practice’s List of Error-Prone Abbreviations, Symbols, and Dose Designations appear throughout the package insert¹. As part of a national campaign to avoid the use of dangerous abbreviations and dose designations, FDA agreed not to approve such error prone abbreviations in the approved labeling of products. Thus, please revise those abbreviations, symbols, and dose designations as follows:
 - i. Revise the abbreviations “>” to read “greater than”, “cc” to read “mL” and “µm” to read “micron”.
4. In section 2.3 (Preparation Instructions)
 - a. To help mitigate wrong administration errors, we recommend bolding the statement “Must be diluted prior to infusion.”
 - b. To help mitigate medication errors during dilution of the product, we recommend the revision of the statement to read: “Defitelio should be diluted in 5% Dextrose Injection, USP or 0.9% Sodium Chloride, USP to a concentration of 4 mg/mL to 20 mg/mL. The diluted infusion should be administered over 2 hours. The total dose and volume of infusion should be determined based on the individual patient’s baseline weight (weight prior to the preparative regimen for HSCT).

¹ ISMP’s List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2015 [cited 2015 October 21]. Available from: <http://www.ismp.org/tools/errorproneabbreviations.pdf>.

- c. Remove the statement (b) (4) because it might be confusing and could lead to errors in calculating the final volume required.
- d. To mitigate the potential for preparation errors, we recommend to revise the instructions for preparation as follows:
 - i. Determine the dose (mg) and number of vials of Defitelio based on the individual patient's baseline weight (weight prior to the preparation regimen for HSCT).
 - ii. Calculate the volume of Defitelio needed, withdraw this amount from the vial and add it to an infusion bag containing 0.9% Sodium Chloride injection or 5% Dextrose injection for each dose to make a final concentration of 4 mg/mL to 20 mg/mL.
 - iii. Gently mix the solution for infusion.
 - iv. After dilution and prior to use, visually inspect the solution for particulate matter. Only clear solutions without visible particles should be used. Depending on the type and amount of diluent, the color of the diluted solution may vary from colorless to light yellow.

4.2 RECOMMENDATIONS FOR THE JAZZ PHARMACEUTICALS, INC

We recommend the following be implemented prior to approval of this NDA:

A. Container label

1. The established name is not commensurate to the prominence of the proprietary name as per CFR 201.10(g) (2)². Revise the presentation of the proprietary name to use title case (i.e. Defitelio) and ensure that the established name is at least ½ the size of the proprietary name and commensurate in prominence to the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features per CFR 201.10(g)(2).
2. Revise the presentation of the established name to include the finished dosage form per USP General Chapter <1> injections³. For example:

Defitelio

² 21 CFR part 201

³ USP General Chapter <1> Injections

(Defibrotide) Injection

3. Provide adequate space between the numerical dose and the unit of measure for increased readability.
 4. Add statement [REDACTED] (b) (4) Discard unused portion” to the principal display panel (PDP) because the PI states not to re-use partially used vials.
- B. Carton labeling
1. See A.1 through A.4 and revise the carton labeling accordingly.
 2. Revise the quantity statement from [REDACTED] (b) (4) to read [REDACTED] (b) (4)
 3. Decrease the font of the “Rx only” statement and consider placing on the side panel, as currently this statement is more prominent than other important information on the PDP.
 4. Add the warning statement “Must be diluted before intravenous infusion” to minimize the risk of the product being administered with dilution.
 5. The lot number and expiration date appear to be omitted from the carton labeling. We recommend adding the lot number and expiration date to ensure this critical information is available and to minimize the risk of the patient taking expired medications.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Defitelio that Jazz Pharmaceuticals, Inc. submitted on July 31, 2015.

Table 2. Relevant Product Information for Defitelio	
Initial Approval Date	N/A
Active Ingredient	Defibrotide
Indication	Defitelio is indicated for the treatment of patients with hepatic veno-occlusive disease (VOD), also known as sinusoidal obstructions syndrome (SOS), (b) (4) following hematopoietic stem-cell transplantation (HSCT).
Route of Administration	Intravenous
Dosage Form	Solution
Strength	200 mg/2.5 mL
Dose and Frequency	The recommended dose is 6.25 mg/kg given as a 2 hour infusion every 6 hours. Administer Defitelio for a minimum of 21 days. If after 21 days signs and symptoms of hepatic VOD have not resolved, continue Defitelio until resolution.
How Supplied	Defitelio is supplied in single-use, clear glass vial. Each carton of Defitelio contains 10 vials.
Storage	Store unused vials of Defitelio at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F). (b) (4)

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On October 8, 2015, we searched the L: drive and AIMS using the terms, Defitelio to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified one previous proprietary name review⁴. There were no previous labeling reviews found.

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⁴ Rutledge, M. Proprietary Name Review for Defitelio (IND 62118 and NDA 208114). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 SEPT 8. 29 p. RCM No.: 2015-80410.

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NICOLE B GARRISON
10/27/2015

YELENA L MASLOV
10/28/2015