CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761179Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 129622

MEETING MINUTES

Jazz Pharmaceuticals Ireland Limited
c/o Jazz Pharmaceuticals, Inc.
Attention: Wheatley Spence, MS
Senior Director, Global Regulatory Strategy
2005 Market Street, Suite 2100
Philadelphia, PA 19103

Dear Ms. Spence:[1]

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for JZP-458.

We also refer to the teleconference between representatives of your firm and the FDA on March 29, 2021. The purpose of the Pre-BLA meeting was to discuss a complete list of the remaining pieces of the cross-functional plan and to align with FDA on proposed submission timing and proposed content to optimally support FDA review.

A copy of the official minutes of the teleconference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Esther Park, Senior Regulatory Health Project Manager, at (301) 796-2811.

Sincerely,

{See appended electronic signature page}

Donna Przepiorka, MD, PhD
Clinical Team Leader
Division of Hematologic Malignancies I
Office of Oncologic Diseases
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Type:	A
Meeting Category:	Pre-BLA
Meeting Date and Time:	Monday, March 29, 2021; 3:00 – 4:00 PM (ET)
Meeting Location:	Teleconference
Application Number:	IND 129622
Product Name:	JZP-458
Indication:	For use as a component of a multi-agent chemotherapeutic regimen for the treatment of acute lymphoblastic leukemia (ALL) and lymphoblastic lymphoma (LBL) in adult and pediatric patients aged > 1 year who have developed hypersensitivity or silent inactivation to *E. coli*-derived asparaginase
Sponsor Name:	Jazz Pharmaceuticals, Inc.
Regulatory Pathway:	351(a) of the Public Health Service Act
Meeting Chair:	Donna Przepiorka, MD, PhD
Meeting Recorder:	Esther Park, PharmD

FDA ATTENDEES

Office of Oncologic Diseases (OOD)/Division of Hematologic Malignancies I (DHMI)
R. Angelo de Claro, MD, Division Director
Donna Przepiorka, MD, PhD, Clinical Team Leader
Cara Rabik, MD, PhD, Clinical Reviewer

Office of Regulatory Operations (ORO)/Division of Regulatory Operations for Oncologic Diseases/Hematologic Malignancies I
Amy Baird, Chief, Project Management Staff
Esther Park, PharmD, Senior Regulatory Health Project Manager

Office of Clinical Pharmacology (OCP)/Division of Cancer Pharmacology I
Olanrewaju Okusanya, PharmD, MS, Acting Deputy Director
Xiling Jiang, PhD, Acting Clinical Pharmacology Team Leader
Lauren Price, PharmD, Clinical Pharmacology Reviewer

OCP/Division of Pharmacometrics
Lian Ma, PhD, Pharmacometrics Team Leader
Liang Li, PhD, Pharmacometrics Reviewer

Office of Biotechnology Products (OBP)/Division of Biotechnology Review and Research III
Susan Kirshner, PhD, Review Chief
Zhenzhen Liu, PhD, Application Technical Lead
Mekonnen LemmaDeChassa, PhD, Product Quality Reviewer

Office of Pharmaceutical Manufacturing Assessment (OPMA)/Division of Biotechnology Manufacturing
Virginia Carroll, PhD, Senior Pharmaceutical Quality Assessor
Michael Shanks, BSc, Interdiscipline Scientist, Biologist

Office of Study Integrity and Surveillance/Division of Generic Drug Study Integrity
Stanley Au, PharmD, BCPS, Lead Pharmacologist

Office of Program and Regulatory Operations (OPRO)
Teshara Bouie, Acting Quality Assessment Lead

SPONSOR ATTENDEES

Robert Iannone, MD, MSCE, Executive Vice President, Research and Development
Punam Sandhu, PhD, Executive Director, Global Regulatory Affairs
Wheatley Spence, MS, Senior Director, Regulatory Strategy
Bhumika Katudia, MS, MBA, Senior Manager, Regulatory Strategy
Jeff McLaren, MSc, Director, Regulatory Affairs Labeling
Robin Hume, MS, RAC, Global Molecule Leader, Asparaginase Franchise
Jeffrey Silverman, PhD, FAAPS, Vice President, Early Development
Tong Lin, PhD, Director, Clinical Pharmacology
Charlene Bruno, MS, Director, Global Regulatory CMC
Austin Power, MSc, Senior Director, Biologics Development
Anne Borgman, MD, Vice President, Therapeutic Area Head, Hematology-Oncology
Mi Rim Choi, MD, Executive Medical Director, Clinical Development Hematology/Oncology; Global Development Leader
Debra Feldman, MD, Vice President, Pharmacovigilance, Drug Safety & Pharmacovigilance
Etsuko Aoki, MD, PhD, Associate Director, Medical Safety, Drug Safety & Pharmacovigilance
Alka Joshi, PhD, Head of Biometrics
Suzanne Swann, PhD, Senior Director, Biostatistics, Biometrics
Michelle Zanette, MS, Director, Biostatistics, Biometrics
Aubri Charboneau, MSCR, PharmD, PhD, Associate Director, Medical Writing, Regulatory Affairs
Lewis B. Silverman, MD, Children's Oncology Group (COG)/Dana Farber Cancer Institute; Boston, (b) (4)
(b) (4)

(b) (4)

1.0 BACKGROUND

JZP-458, a recombinant *Erwinia chrysanthemia* asparaginase, is being developed by Jazz Pharmaceuticals as a component of a multi-agent chemotherapeutic regimen for the treatment of patients who developed hypersensitivity to *E. coli*-derived asparaginase during treatment for ALL or LBL. Orphan Designation was granted for asparaginase erwinia chrysanthemi in 1986. Fast Track Designation was granted on October 24, 2019. An iPSP was agreed on April 21, 2020. FDA provided initial formal advice on May 17, 2016, in response to a Type B PIND request, and in seven additional meetings or Written Responses Only thereafter. An RTOR submission plan was agreed upon on December 18, 2020, and the first portion of BLA 761179 was received the same date. The completion of the BLA submission is expected on April 12, 2021.

On February 25, 2021, the Sponsor requested a Pre-BLA meeting to 1) gain agreement on the late submission components of the BLA, 2) discuss the adequacy of the package to support recommended dosing, and 3) agree on activities to support the initiation of the Pre-License Inspection (PLI).

FDA sent Preliminary Comments to Jazz Pharmaceuticals on March 25, 2021.

2.0 DISCUSSION

2.1. Clinical

Question 1: *Does the Agency agree that the following data from the ongoing Study JZP458-201 are sufficient to support approval of 25 mg/m^2 JZP-458 administered intramuscularly Monday and Wednesday and 50 mg/m^2 JZP-458 on Friday for a total of 6 doses every 2 weeks for this indication?*

- *SDTM + ADaM data package and TFLs for Cohorts 1a and 1b (data cut-off: 14 October 2020) (submitted on 10 February 2021)*

- *BLA submission (on 12 April 2021) with data cut-off of 14 October 2020:*
  - *PPK modeling and simulation data for 25/25/50 mg/m^2 MWF based on data from Cohorts 1a (N = 32) and 1b (N = 53)*
  - *Observed efficacy data from Cohorts 1a (N = 32) and 1b (N = 53)*
  - *PD data from Cohorts 1a (N = 32) and 1b (N = 53)*
  - *Safety data from Cohorts 1a (N = 33) and 1b (N = 53)*
  - *Immunogenicity data from Cohorts 1a (N = 33) and 1b (N = 53)*

- *A standalone submission of the Updated PPK Modeling and Simulation Report (based on data from IM Cohorts 1a [N = 32], 1b [N = 53], and 1c [N = 16]) to the BLA in late April 2021 (note: this same report will be submitted earlier to the IND on 19 March 2021 [ie, prior to the pre-BLA meeting])*

- *SDTM + ADaM data package and TFLs for Cohorts 1a, 1b, and 1c (data cut-off: 11 January 2021) (to be submitted to the BLA at the end of May 2021)*

- *60-day Update Report with data cut-off of 11 January 2021 (to be submitted to the BLA at the end of June 2021):*
  - *Available efficacy, PK (SAA), PD, and immunogenicity data from Cohorts 1a (N = 32) and 1b (N = 53)*
  - *Efficacy, PK (SAA), PD, and immunogenicity data from Cohort 1c (N = 16)*
  - *Safety data from Cohorts 1a (N = 33), 1b (N = 53), and 1c (N = 16)*
  - *Summary of the updated PPK modeling and simulation analysis based on data from Cohorts 1a (N = 32), 1b (N = 53), and 1c (N = 16) (based on the updated PPK modeling and simulation report submitted to the BLA in late April 2021, as described above)*

FDA Response to Question 1:
The proposed data package is acceptable to support review of the proposed 25/25/50 mg/m^2 IM MWF x 6 dosing regimen. Whether the totality of data support approval of the proposed dosing regimen is a review issue.

We strongly encourage you to submit the updated population PK report, 60-day update report, and updated safety, PD, PK, and immunogenicity data through the 11 Jan 2021 data cut-off (including the first 17 patients enrolled in Cohort 1c) as soon as possible to facilitate a timely review.

Per the meeting package, Study JZP458-201 Cohort 1c has enrolled 47 out of a planned 51 patients as of 24 Feb 2021. Provide a plan for submission of safety, PD, PK, and immunogenicity data from all patients enrolled to Cohort 1c.

Discussion: **The Sponsor asked if the data package as described in Question 1 was sufficient or if additional data would be needed to support the BLA. FDA indicated that the PK data as outlined were sufficient to support review, and the adequacy of the safety data would be a review issue depending on the recommended dose.**

Question 2: *Jazz is pursuing an IM dosing regimen (25/25/50 mg/m^2 MWF) in the label to support the majority of current ALL dosing protocols in North America; however, as an alternative, Jazz also has an adequate data package to support 48-hour dosing. Jazz would like to confirm that the Agency is in agreement on the*

complete data set that would support the alternate dosing regimen option: 25 mg/m2 JZP-458 administered every 48 hours.

Does the Agency agree that the following data from ongoing Study JZP458-201 are sufficient to support approval of 25 mg/m^2 JZP-458 administered intramuscularly every 48 hours for a total of 7 doses every 2 weeks for the proposed indication?

- *SDTM + ADaM data package and TFLs for Cohorts 1a and 1b (data cut-off: 14 October 2020) (submitted on 10 February 2021)*

- *BLA submission (on 12 April 2021) with data cut-off of 14 October 2020:*
  - *PPK modeling and simulation results for 25 mg/m^2 every 48 hours based on data from Cohorts 1a (N = 32) and 1b (N = 53)*
  - *Observed efficacy data from Cohorts 1a (N = 32) and 1b (N = 53)*
  - *PD data from Cohorts 1a (N = 32) and 1b (N = 53)*
  - *Safety and immunogenicity data from Cohorts 1a (N = 33) and 1b (N = 53)*

- *SDTM + ADaM data package and TFLs for Cohorts 1a, 1b, and 1c (data cut-off: 11 January 2021) (to be submitted to the BLA at the end of May 2021)*

- *60-day Update Report with data cut-off of 11 January 2021 (to be submitted to the BLA at the end of June 2021):*
  - *Available efficacy, PK (SAA), PD, and immunogenicity data from Cohorts 1a (N = 32) and 1b (N = 53)*
  - *Efficacy, PK (SAA), PD, and immunogenicity data from Cohort 1c (N = 16)*
  - *Safety data from Cohorts 1a (N = 33), 1b (N = 53), and 1c (N = 16)*

FDA Response to Question 2:
The proposed data package is acceptable to support review of the proposed 25 mg/m^2 IM Q48H x 7 dosing regimen. Whether the totality of data support approval of the proposed dosing regimen is a review issue. See also the response to Question 1.

Discussion: **There was no discussion.**

Question 3: *Jazz would like to confirm the content (including any late submission components for BLA) for the 60-day Update is sufficient to allow completion of the review of IM data and support a determination of marketing approval of IM JZP-458.*

Proposed BLA Submission Timing	Late Submission Components
Late April 2021	Updated PPK Modeling and Simulation Analysis Report, based on data from the following: – Cohorts 1a (N = 32) and 1b (N = 53) (data cut-off: 14 October 2020) – Cohort 1c (N = 16) (data cut-off: 11 January 2021)
End of May 2021 (60-day Update data package)	SDTM + ADaM data package and TFLs for Cohorts 1a (N = 33), 1b (N = 53), and 1c (N = 17, including 1 participant who was never dosed) as of 11 January 2021
End of June 2021 (60-day Update Report)	Updated Cohort 1a (N = 33) safety data through the data cut-off of 11 January 2021 plus available efficacy, PK, PD (L-asparagine and L-glutamine concentrations), and immunogenicity data
	Updated Cohort 1b (N = 53) safety data through the data cut-off of 11 January 2021 plus available efficacy, PK, PD (L-asparagine and L-glutamine concentrations), and immunogenicity data
	Cohort 1c (N = 17, including 1 participant who was never dosed) efficacy, PK, PD (L-asparagine and L-glutamine concentrations, immunogenicity, and safety data (data cut-off: 11 January 2021)

a. *Does the Agency agree with Jazz's proposal to submit an Updated PPK Modeling and Simulation Analysis Report, based on data from Cohorts 1a (N = 32), 1b (N = 53), and 1c (N = 16), as a standalone submission to the BLA in late April 2021 (note: this same report will be submitted earlier to the IND on 19 March 2021 [ie, prior to the pre-BLA meeting])?*

FDA Response to Question 3a:

No. The Updated PPK Modeling and Simulation Analysis Report is complete and has been submitted to the IND. Submit this report to the BLA along with all necessary supportive documents and datasets as soon as possible.

Discussion: **The Sponsor provided a tabular summary of a revised timeline for submission of the BLA, the 60-day update, and one additional late submission of study reports with a data cut-off of January 11, 2021. FDA agreed with the revised timeline and the late submission as outlined in Table 1 of the additional information submitted by email and reproduced below.**

Table 1: Upcoming BLA Submissions with Revisions based on FDA Requests

Proposed BLA Submission Timing	Submission Type	Submission Components
~~Late April 2021~~ *March 26, 2021 (new)*	Original BLA	Initial Cohort 1c PPK Modeling and Simulation Report (Sensitivity analysis) and associated datasets, based on data from the following:

Proposed BLA Submission Timing	Submission Type	Submission Components
		– Cohorts 1a (N = 32) and 1b (N = 53) (data cut-off: October 14, 2020) – Cohort 1c (N = 16) (data cut-off: January 11, 2021)
April 12, 2021	Original BLA	• Final Cohort 1a and 1b Full PPK Report (detailed descriptions and conclusions, plus model qualifications, plus Exposure-Response/Safety analyses) and associated datasets (Cohorts 1a [N = 32] and 1b [N = 53], data cut-off: October 14, 2020) • JZP458-201 CSR Version 01 (data from Cohorts 1a [N = 33] and 1b [N = 53] as of October 14, 2020) • BLA Modules 2.2, 2.4, and 2.6
*Late April, 2021** *(new)*	Original BLA (Final BLA submission)	• JZP458-101 CSR Addendum (updated SAA data per FDA IR) • BLA Modules 2.7.1, 2.7.2, 2.7.3, 2.7.4, 2.7.5, 2.7.6, and 2.5 (with updated JZP458-101 SAA data per FDA IR and data for Study JZP458-201 as of October 14, 2020) • Integrated Summary of Immunogenicity (ISI) in Module 5.3.5.3
End of May 2021 (60-day Update data package)	Late Submission	SDTM + ADaM data package and TFLs for Cohorts 1a (N = 33), 1b (N = 53), and 1c (N = 17, including 1 participant who was never dosed) as of January 11, 2021
Late June 2021 (Update Report)	Late Submission	• JZP458-201 CSR Version 02 (data cut-off: January 11, 2021) • Updated ISI Data to be provided in the documents listed above, as applicable, are as follows: Updated Cohort 1a (N = 33) safety data through the data cut-off of January 11, 2021 plus available efficacy, PK, PD (L-asparagine and L-glutamine concentrations), and immunogenicity data
		Updated Cohort 1b (N = 53) safety data through the data cut-off of January 11, 2021 plus available efficacy, PK, PD (L-asparagine and L-glutamine concentrations), and immunogenicity data
		Cohort 1c (N = 17), including 1 participant who was never dosed) efficacy, PK, PD (L-asparagine and L-glutamine concentrations, immunogenicity, and safety data (data cut-off: January 11, 2021)

* pending on-time completion of dataset transfer from Vendor

Additionally, FDA confirmed that they received the PPK datasets on March 26, 2021.

b. *Does the Agency agree with the proposed content plan for the 60-day Update following the initial BLA submission for IM JZP-458?*

FDA Response to Question 3b:
Yes. See also the responses to Questions 1 and 2.

Discussion: **There was no discussion.**

c. *Does the Agency agree that the proposed 60-day Update provides adequate safety and immunogenicity data for the Agency to complete their review and approval of IM JZP-458?*

FDA Response to Question 3c:
The adequacy of the contents of the update will be a review issue. See also the response to Question 4.

Discussion: **There was no discussion.**

2.2. Clinical Pharmacology

Question 4: *Following the initial analysis of available immunogenicity data (as of 14 October 2020) from Cohorts 1a and 1b in Study JZP458-201 for the BLA submission, Jazz plans to submit updated immunogenicity data (from Cohorts 1a, 1b, and 1c) in the 60-day update, and the final immunogenicity data from this study in a final updated Integrated Summary of Immunogenicity (ISI) after the end of the study (post LPLV). Does the Agency agree with this plan for reporting immunogenicity data from Study JZP458-201?*

FDA Response to Question 4:
The ISI should be iteratively updated for future BLA submissions based on updated data cut-off dates. Submission of an updated ISI should not be delayed until after completion of Study JZP458-201.

Discussion: **The Sponsor will submit the original ISI with a data cut-off of October 14, 2021 in the late April package and the updated ISI with the 60-day update report in June 2021. FDA agreed to this plan.**

2.3. Labeling

Question 5: *Does the Agency agree with the proposed indication for JZP-458?*

FDA Response to Question 5:
The wording of the indication will be a review issue.

Discussion: **There was no discussion.**

Question 6: *Does FDA agree with the proposed presentation for modeling and simulation data within Section 14, Clinical Studies of the USPI?*

FDA Response to Question 6:
The contents of the USPI will be a review issue.

Discussion: **There was no discussion.**

2.4. Regulatory

Question 7: *Does the Agency agree to the plan and proposed date for the AOM?*

FDA Response to Question 7:
No. We currently have the AOM scheduled for Thursday, April 15, 2021 from 11:30 AM to 12:30 PM.

Discussion: **Based on a new late April submission date, the Sponsor confirmed that the AOM can be scheduled for Friday, May 7, 2021, from 2:30 to 3:30 PM (ET).**

Question 8: *Does FDA agree with Jazz's plan to provide the SDTM +ADaM data package and the TFLs supporting the BLA 60-Day Update Report separately ahead of the planned abbreviated Interim CSR described within this meeting package?*

FDA Response to Question 8:
See response to Question 3.

Discussion: **There was no discussion.**

2.5. CMC

Question 9: *If an onsite PLI* (b) (4) *will not be possible within 2Q2021, can the Agency advise what alternate approaches can be explored to support review and approval of the application within the PDFUA review timelines?*

FDA Response to Question 9:
FDA anticipates completion of any needed pre-license inspections during the BLA review cycle. FDA will continue to monitor the public health situation and communicate with the relevant manufacturing facilities to coordinate the inspections as needed.

Discussion: **The Sponsor recognized that an inspection is planned at (b) (4) and asked if an inspection was planned for the drug product manufacturing facility, (b) (4) FDA indicated that if a pre-license inspection at (b) (4) is needed, the FDA will contact the facility during the review cycle. The Sponsor agreed to provide a current manufacturing schedule this week.**

ADDITIONAL CLINICAL COMMENTS

1. If you are planning to use your current Orphan Designation for acute lymphoblastic leukemia/lymphoma for this submission, please insert the designation number in Line 15A of the Form 356h.

2. FDA has discussed your application with Project Orbis partner countries, and several countries have expressed interest in reviewing the application under a Project Orbis Type B or Type C submission plan. Please fill in the table below to describe your global submission strategy:

Country	Submission Plan*
Australia	
Canada	
Singapore	
Switzerland	

*Include Sponsor name for each country and the submission timeline. Example: [Sponsor name or designee] to submit on MM/DD/YYYY.

Discussion: **There was no discussion.**

3.0 OTHER IMPORTANT MEETING INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. The content of a complete application was agreed upon as indicated in the Discussion under Questions 1 and 3a.

- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- A preliminary discussion was held on the need for a REMS, other risk management actions and, where applicable, the development of a Formal Communication Plan and it was concluded that the need for a REMS will be a review issue.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. The only agreed-upon late component was the June submission of the study reports with analyses of the datasets included in the May 60-day update.

Prominently identify each submission containing your late component(s) with the following wording in bold capital letters at the top of the first page of the submission:

BLA NUMBER: LATE COMPONENT - BIOMETRICS
BLA NUMBER: LATE COMPONENT - CLINICAL
BLA NUMBER: LATE COMPONENT - CLINICAL PHARMACOLOGY
BLA NUMBER: LATE COMPONENT - NONCLINICAL
BLA NUMBER: LATE COMPONENT - QUALITY

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that any original marketing application for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA has determined to be substantially relevant to the growth or progression of a pediatric cancer) that are submitted on or after August 18, 2020, contain reports of molecularly targeted pediatric cancer investigations. See link to list of relevant molecular targets below. These molecularly targeted pediatric cancer investigations must be “designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling” (section 505B(a)(3)). Applications for drugs or biological products for which orphan designation has been granted and which are subject to the requirements of section 505B(a)(1)(B), however, will not be exempt from PREA (see section 505B(k)(2)) and will be required to include plans to conduct the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

Under section 505B(e)(2)(A)(i) of the FD&C Act, you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase 2 (EOP2) meeting, or such other time as agreed upon with FDA. (In the absence of an EOP2 meeting, refer to the draft guidance below.) The iPSP must contain an outline of the pediatric assessment(s) or molecularly targeted pediatric cancer investigation(s) that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation; and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*. For the latest version of the molecular target list, please refer to FDA.gov.[2]

FDARA REQUIREMENTS

Sponsors planning to submit original applications on or after August 18, 2020 or sponsors who are uncertain of their submission date may request a meeting with the Oncology Center of Excellence Pediatric Oncology Program to discuss preparation of the sponsor's initial pediatric study plan (iPSP) for a drug/biologic that is intended to treat a serious or life-threatening disease/ condition which includes addressing the amendments to PREA (Sec. 505B of the FD &C Act) for early evaluation in the pediatric population of new drugs directed at a target that the FDA deems substantively relevant to the growth or progression of one or more types of cancer in children. The purpose of these meetings will be to discuss the Agency's current thinking about the relevance of a specific target and the specific expectations for early assessment in the pediatric population unless substantive justification for a waiver or deferral can be provided.

Meetings requests should be sent to the appropriate review division with the cover letter clearly stating "**MEETING REQUEST FOR PREPARATION OF iPSP MEETING UNDER FDARA.**" These meetings will be scheduled within 30 days of meeting request receipt. The Agency strongly advises the complete meeting package be submitted at the same time as the meeting request. Sponsors should consult the guidance for industry, *Formal Meetings Between the FDA and Sponsors or Applicants*, to ensure open lines of dialogue before and during their drug development process.

In addition, you may contact the OCE Subcommittee of PeRC Regulatory Project Manager by email at OCEPERC@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[3]

[2] https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology
[3] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[4] and Pregnancy and Lactation Labeling Final Rule[5] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

[4] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[5] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				
(2)				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				
(2)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[6] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[7]. Submit all related

[6] https://www.fda.gov/media/84223/download
[7] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and

manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

NONPROPRIETARY NAME

On January 13, 2017, FDA issued a final guidance for industry *Nonproprietary Naming of Biological Products*, stating that, for certain biological products, the Agency intends to designate a proper name that includes a four-letter distinguishing suffix that is devoid of meaning.

Please note that certain provisions of this guidance describe a collection of information and are under review by the Office of Management and Budget under the Paperwork Reduction Act of 1995 (PRA). These provisions of the guidance describe the submission of proposed suffixes to the FDA, and a sponsor's related analysis of proposed suffixes, which are considered a "collection of information" under the PRA. FDA is not currently implementing provisions of the guidance that describe this collection of information.

However, provisions of the final guidance that do not describe the collection of information should be considered final and represent FDA's current thinking on the nonproprietary naming of biological products. These include, generally, the description of the naming convention (including its format for originator, related, and biosimilar biological products) and the considerations that support the convention.

To the extent that your proposed 351(a) BLA is within the scope of this guidance, FDA will assign a four-letter suffix for inclusion in the proper name designated in the license at such time as FDA approves the BLA.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were no action items.

6.0 ATTACHMENTS AND HANDOUTS

The Sponsor's response to the Agency's meeting preliminary comments is appended to these minutes.

Jazz Pharmaceuticals Ireland (Jazz) is providing this response to the Type A pre-BLA meeting preliminary comments received from the FDA on March 25, 2021, in advance of the Type A meeting scheduled for March 29, 2021 at 3:00-4:00PM (ET). This meeting is scheduled to discuss and reach agreement on Jazz's proposal on the submission components of the BLA, discuss the adequacy of the package to support recommended dosing, and agree on activities to support the initiation of the Pre-License Inspection (PLI) for the proposed biologics license application (Meeting Category: Pre-BLA). The clinical briefing book was submitted to IND 129,622 JZP-458 on February 25, 2021 (SN0078).

For the purpose of the FDA Meeting, Jazz is providing the response to the following questions:

- Question 1
- Question 3a
- Question 4
- Question 7
- Question 9
- Additional clinical comments
- Other Important Meeting Information

For the meeting discussion, Jazz would like to focus on the following questions:

- Question 1
- Question 7
- Question 9

FDA PRELIMINARY COMMENTS AND SPONSOR (JAZZ) RESPONSE

Question 1: *Does the Agency agree that the following data from the ongoing Study JZP458-201 are sufficient to support approval of 25 mg/m^2 JZP-458 administered intramuscularly Monday and Wednesday and 50 mg/m^2 JZP-458 on Friday for a total of 6 doses every 2 weeks for this indication?*

- *SDTM + ADaM data package and TFLs for Cohorts 1a and 1b (data cut-off: 14 October 2020) (submitted on 10 February 2021)*
- *BLA submission (on 12 April 2021) with data cut-off of 14 October 2020:*
    - *PPK modeling and simulation data for 25/25/50 mg/m^2 MWF based on data from Cohorts 1a (N = 32) and 1b (N = 53)*
    - *Observed efficacy data from Cohorts 1a (N = 32) and 1b (N = 53*
    - *PD data from Cohorts 1a (N = 32) and 1b (N = 53)*
    - *Safety data from Cohorts 1a (N = 33) and 1b (N = 53)*
    - *Immunogenicity data from Cohorts 1a (N = 33) and 1b (N = 53)*
- *A standalone submission of the Updated PPK Modeling and Simulation Report (based on data from IM Cohorts 1a [N = 32], 1b [N = 53], and 1c [N =16]) to the BLA in late April*

2021 (note: this same report will be submitted earlier to the IND on 19 March 2021 [i.e., prior to the pre-BLA meeting])

- *SDTM + ADaM data package and TFLs for Cohorts 1a, 1b, and 1c (data cutoff: 11 January 2021) (to be submitted to the BLA at the end of May 2021)*
- *60-day Update Report with data cut-off of 11 January 2021 (to be submitted to the BLA at the end of June 2021):*
    - *Available efficacy, PK (SAA), PD, and immunogenicity data from*
    - *Cohorts 1a (N = 32) and 1b (N = 53)*
    - *Efficacy, PK (SAA), PD, and immunogenicity data from Cohort 1c (N =16)*
    - *Safety data from Cohorts 1a (N = 33), 1b (N = 53), and 1c (N = 16)*
    - *Summary of the updated PPK modeling and simulation analysis based on data from Cohorts 1a (N = 32), 1b (N = 53), and 1c (N = 16) (based on the updated PPK modeling and simulation report submitted to the BLA in late April 2021, as described above)*

FDA Preliminary comment: The proposed data package is acceptable to support review of the proposed 25/25/50 mg/m^2 IM MWF x 6 dosing regimen. Whether the totality of data support approval of the proposed dosing regimen is a review issue.

We strongly encourage you to submit the updated population PK report, 60-day update report, and updated safety, PD, PK, and immunogenicity data through the 11 Jan 2021 data cut-off (including the first 17 patients enrolled in Cohort 1c) as soon as possible to facilitate a timely review.

Per the meeting package, Study JZP458-201 Cohort 1c has enrolled 47 out of a planned 51 patients as of 24 Feb 2021. Provide a plan for submission of safety, PD, PK, and immunogenicity data from all patients enrolled to Cohort 1c.

Jazz Response:

Jazz will continue to look for ways in which we can accelerate the timeline for submission of the 60-day update report and updated safety, PK, PD, and immunogenicity data through 11 Jan 2021 cut-off, and submit to the Agency in a timely manner. We anticipate this can be completed in the mid-June timeframe, and will confirm the revised date and submissions expectations as soon as possible.

Jazz intends to pool safety data in the 60-day update report from all 102 patients with available safety data (from Cohort 1a, N= 33), Cohort 1b, N= 53, Cohort 1c, N= 16) and include this in the updated label. This approach provides a robust, longitudinal dataset from all doses studied and includes data from all cohorts, including more information on long-term JZP-458 exposure for most patients.

Jazz will submit all Cohort 1c data as a part of the IM interim CSR at the completion of Part A of the study. This will include data from all patients enrolled to Part A (IM) of the

JZP458-201 study (Cohort 1a, N= 33, Cohort 1b, N= 84, Cohort 1c, N= 52), including follow up from all courses of asparaginase received in the study in 2022 contingent on when the last patient completes their last course.

Does the Agency agree with the proposed plan and timeframe as proposed above?

Jazz would also like to reference the response submitted to BLA 761179 (March 15, 2021email to RPM), which provided timing for the revised JZP458-101 CSR Addendum to provide updated tables for the JZP-458 SAA data. As these data and resulting TFLs are required to be included in the Module 2 summary documents, Jazz has revised the dates for the final BLA submission accordingly to meet FDA request for revised data in the Phase 1 CSR and Module 2 summary documents.

Does the FDA agree with our revised timing and contents for the BLA submission as provided in Table 1?

Table 1: Upcoming BLA Submissions with Revisions based on FDA Requests

Proposed BLA Submission Timing	**Submission Type**	**Submission Components**
~~Late April 2021~~ *March 26, 2021* *(new)*	Original BLA	Initial Cohort 1c PPK Modeling and Simulation Report (Sensitivity analysis) and associated datasets, based on data from the following: – Cohorts 1a (N = 32) and 1b (N = 53) (data cut-off: October 14, 2020) – Cohort 1c (N = 16) (data cut-off: January 11, 2021)
April 12, 2021	Original BLA	• Final Cohort 1a and 1b Full PPK Report (detailed descriptions and conclusions, plus model qualifications, plus Exposure-Response/Safety analyses) and associated datasets (Cohorts 1a [N = 32] and 1b [N = 53], data cut-off: October 14, 2020) • JZP458-201 CSR Version 01 (data from Cohorts 1a [N = 33] and 1b [N = 53] as of October 14, 2020) • BLA Modules 2.2, 2.4, and 2.6
*Late April, 2021** *(new)*	Original BLA (Final BLA submission)	• JZP458-101 CSR Addendum (updated SAA data per FDA IR) • BLA Modules 2.7.1, 2.7.2, 2.7.3, 2.7.4, 2.7.5, 2.7.6, and 2.5 (with updated JZP458-101 SAA data per FDA IR and data for Study JZP458-201 as of October 14, 2020) • Integrated Summary of Immunogenicity (ISI) in Module 5.3.5.3
End of May 2021 (60-day Update data package)	Late Submission	SDTM + ADaM data package and TFLs for Cohorts 1a (N = 33), 1b (N = 53), and 1c (N = 17, including 1 participant who was never dosed) as of January 11, 2021
Late June 2021 (Update Report)	Late Submission	• JZP458-201 CSR Version 02 (data cut-off: January 11, 2021) • Updated ISI

Proposed BLA Submission Timing	Submission Type	Submission Components
		Data to be provided in the documents listed above, as applicable, are as follows: Updated Cohort 1a (N = 33) safety data through the data cut-off of January 11, 2021 plus available efficacy, PK, PD (L-asparagine and L-glutamine concentrations), and immunogenicity data
		Updated Cohort 1b (N = 53) safety data through the data cut-off of January 11, 2021 plus available efficacy, PK, PD (L-asparagine and L-glutamine concentrations), and immunogenicity data
		Cohort 1c (N = 17), including 1 participant who was never dosed) efficacy, PK, PD (L-asparagine and L-glutamine concentrations, immunogenicity, and safety data (data cut-off: January 11, 2021)

* pending on-time completion of dataset transfer from Vendor

Question 3a: *Does the Agency agree with Jazz's proposal to submit an Updated PPK Modeling and Simulation Analysis Report, based on data from Cohorts 1a (N =32), 1b (N = 53), and 1c (N = 16), as a standalone submission to the BLA in late April 2021 (note: this same report will be submitted earlier to the IND on 19 March 2021 [i.e., prior to the pre-BLA meeting])?*

FDA Preliminary comment: No. The Updated PPK Modeling and Simulation Analysis Report is complete and has been submitted to the IND. Submit this report to the BLA along with all necessary supportive documents and datasets as soon as possible.

Jazz Response: Jazz acknowledges Agency's feedback and will submit the updated PPK Modeling and Simulation Analysis Report for Cohort 1c including the associated datasets that were submitted to the IND on February 19, 2021 (IND 129622/SN 0083) by March 26, 2021 to the BLA 761179.

Question 4: *Following the initial analysis of available immunogenicity data (as of 14 October 2020) from Cohorts 1a and 1b in Study JZP458-201 for the BLA submission, Jazz plans to submit updated immunogenicity data (from Cohorts 1a, 1b, and 1c) in the 60-day update, and the final immunogenicity data from this study in a final updated Integrated Summary of Immunogenicity (ISI) after the end of the study (post LPLV). Does the Agency agree with this plan for reporting immunogenicity data from Study JZP458-201?*

FDA Preliminary comment: The ISI should be iteratively updated for future BLA submissions based on updated data cut-off dates. Submission of an updated ISI should not be delayed until after completion of Study JZP458-201.

Jazz Response: Jazz agrees that the ISI information should be provided iteratively. Jazz would like to provide the next ISI update at the 60-day update report targeted for June 2021 (listed in Table 1), and will continue to update the ISI for future BLA submissions based on their respective data cut-off dates.

Question 7: *Does the Agency agree to the plan and proposed date for the AOM?*

FDA Preliminary comment: No. We currently have the AOM scheduled for Thursday, April 15, 2021 from 11:30 AM to 12:30 PM.

Jazz Response: Jazz would like to inquire if there are specific topics the Agency would like Jazz to focus on within the meeting slides for the AOM. Currently, Jazz plans to present an overview of the development program for the study JZP458-201, including the CMC update in a 20 min presentation.

Jazz would also like to confirm that the April 15, 2021 date is still in agreement, if the Agency agrees to the new target for final BLA submission of April 28, 2021?

Question 9*: If an onsite PLI of* (b) (4) *will not be possible within 2Q2021, can the Agency advise what alternate approaches can be explored to support review and approval of the application within the PDFUA review timelines?*

FDA Preliminary comment*:* *FDA anticipates completion of any needed pre-license inspections during the BLA review cycle. FDA will continue to monitor the public health situation and communicate with the relevant manufacturing facilities to coordinate the inspections as needed.*

Jazz Response:
Jazz appreciates the Agency's feedback, and recognizes that an inspection is planned at (b) (4) Also, Jazz requests if the Agency can provide any information about an inspection, or an inspection alternative, at the drug product manufacturing facility, (b) (4)

ADDITIONAL CLINICAL COMMENTS

1. *If you are planning to use your current Orphan Designation for acute lymphoblastic leukemia/lymphoma for this submission, please insert the designation number in Line 15A of the Form 356h.*

   Jazz Response: Jazz appreciates the Agency's feedback and would like to provide an update on the pending Orphan Drug Designation status for JZP-458. Jazz is currently working on responding to the deficiency letter dated October 20, 2020, received from the Office of Orphan Products Development (OOPD) on the Orphan Drug Application for JZP-458 (Designation request # DRU-2020-7734).

   Jazz will provide an update to the Agency, upon submission of the response to OOPD that is targeted for submission no later than early April 2021 and receipt of the decision from OOPD.

2. *FDA has discussed your application with Project Orbis partner countries, and several countries have expressed interest in reviewing the application under a Project Orbis Type B or Type C submission plan. Please fill in the table below to describe your global submission strategy:*

Country	***Submission Plan****
Australia	
Canada	
Singapore	
Switzerland	

*Include Sponsor name for each country and the submission timeline. Example: [Sponsor name or designee] to submit on MM/DD/YYYY.

Jazz Response: Jazz appreciates the feedback and interest in joining Project Orbis. Jazz will review the country list as provided in the table above and revert back with the requested information based on filing strategy and timelines in these regions.

(b) (4)

3.0 OTHER IMPORTANT MEETING INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our February 26, 2021 communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA VI. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions and, where applicable, the development of a Formal Communication Plan. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission. Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission. In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities. Information on the Program is available at FDA.gov[1].

Jazz Response:

JZP-458 has a similar risk profile to existing asparaginases that has been well characterized. No specific risks for JZP-458 related to immunogenicity have been identified thus far. Hypersensitivity reactions have been reported but the incidence has been comparable to other asparaginases, and all events have been reported as resolved with standard medical care. JZP-458 is administered by specialists who are familiar with the management of allergic reactions under close observation. Based on these data, Jazz do not anticipate the need for a REMS for JZP-458. The existing risks can be mitigated with appropriate prescriber label information, particularly warnings and precautions as provided in the draft label. Clinical allergic reactions will be monitored through routine pharmacovigilance activities.

[1] https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default htm

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify in a single location, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility. Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h[2]. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h. To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h7 and the guidance for industry, Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

Jazz Response: Jazz acknowledges the Agency's feedback. Jazz will submit the 356h form containing manufacturing sites information in a single location.

[2] https://www.fda.gov/media/84223/download

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DONNA PRZEPIORKA
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