

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***

**761179Orig1s000**

**PRODUCT QUALITY REVIEW(S)**

A Fast track development program for the treatment of patients with ALL/LBL  
who have developed hypersensitivity to *E. coli* derived asparaginase

## Recommendation: Approval

### OPQ EXECUTIVE SUMMARY

BLA Number: 761179  
Assessment Number: 1  
Assessment Date: June 18, 2021

|                         |                                                                                                                                                                        |
|-------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Drug Name/Dosage Form   | RYLAZE (JZP-458, RC-P, asparaginase erwinia chrysanthemi (recombinant)-rywn)                                                                                           |
| Strength/Potency        | 10 mg/0.5 mL solution in a single-dose vial                                                                                                                            |
| Route of Administration | Intra-muscular injection                                                                                                                                               |
| Rx/OTC dispensed        | Rx                                                                                                                                                                     |
| Indication              | Treatment of patients with acute lymphoblastic leukemia (ALL) / lymphoblastic lymphoma (LBL) who have developed hypersensitivity to <i>E.coli</i> derived asparaginase |
| Applicant/Sponsor       | Jazz Pharmaceuticals Ireland Limited                                                                                                                                   |

### Product Overview

JZP-458 is a recombinant crisantaspase (the native asparaginase *Erwinia chrysanthemi*) produced in *Pseudomonas fluorescens*. JZP-458 is a tetrameric 140 kDa enzyme consisting of four 35 kDa subunits. The amino acid sequence and structure of JZP-458 are consistent with those of the *Erwinia chrysanthemi*-derived L-asparaginase, Erwinaze. JZP-458 developed as a component of multi-agent chemotherapy for acute lymphoblastic leukemia (ALL)/Lymphoblastic Lymphoma (LBL) for patients that developed hypersensitivity to *E-coli* derived L-Asparaginase. JZP-458 catalyzes L-asparagine to L-aspartic acid and ammonia. The mechanism of action of JZP-458 is based on the killing of leukemic cells due to depletion of plasma asparagine. Leukemic cells with low expression of asparagine synthetase have a reduced ability to synthesize asparagine, and therefore depend on an exogenous source of asparagine for survival.

### Quality Assessment Team

| Discipline                  | Assessor                                                                                                   | Branch/Division                                                     |
|-----------------------------|------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------|
| Product Quality (DS and DP) | Mekonnen Lemma Dechassa                                                                                    | CDER/OPQ/OBP/DBRR III                                               |
| Immunogenicity              | Mekonnen Lemma Dechassa                                                                                    | CDER/OPQ/OBP/DBRR III                                               |
| Labeling                    | CAPT Vicky Borders Hemphill                                                                                | CDER/OPQ/OBP                                                        |
| Facility                    | Michael Shanks                                                                                             | CDER/OPQ/OPMA/DBM                                                   |
| Microbiology                | Reyes Candau-Chacon                                                                                        | CDER/OPQ/OPMA/DBM                                                   |
| Team Lead                   | Zhenzhen Liu (Product quality)<br>Zhenzhen Liu (Immunogenicity)<br>Virginia Carroll (Micro and Facilities) | CDER/OPQ/OBP/DBRR III<br>CDER/OPQ/OBP/DBRR III<br>CDER/OPQ/OPMA/DBM |
| Application Technical Lead  | Zhenzhen Liu                                                                                               | CDER/OPQ/OBP/DBRR III                                               |
| OPQ RBPM                    | Teshara Bouie                                                                                              | CDER/OPQ/OPRO/DRBPMI/RBPMB2                                         |

## Multidisciplinary Assessment Team

| Discipline                   | Assessor                                                                                                         | Office / Division                                              |
|------------------------------|------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------|
| RPM                          | Esther Park                                                                                                      | CDER/OND/ORO/OROOD                                             |
| Cross-disciplinary Team Lead | Donna Przepiorka                                                                                                 | CDER/OND/OD/DHM1                                               |
| Medical Officer              | Cara Rabik                                                                                                       | CDER/OND/OD/DHM1                                               |
| Pharmacology/Toxicology      | Michael Manning / Brenda Gehrke                                                                                  | CDER/OND/OD/DHOT                                               |
| Clinical Pharmacology        | Lauren Price / Xiling Jiang, Lanre Okusanya (TL)<br>Liang Li / Lian Ma (TL)<br>Melkamu Getie Kebtie / Stanley Au | CDER/OTS/OCPI/DCPI<br>CDER/OTS/OCPI/DPM<br>CDER/OTS/OSIS/DGDSI |
| Statistics                   | Haiyan Chen / Jonathon Vallejo, Lisa Rodriguez                                                                   | CDER/OTS/OB/DBIX                                               |

### 1. Names:

- Proprietary Name: RYLAZE
- Trade Name: RYLAZE
- Non-Proprietary Name/USAN: asparaginase erwinia chrysanthemi (recombinant)-rywn
- CAS Name: not provided
- Common Name: JZP-458
- INN name: not provided
- OBP systematic name:  
PROT P06608 (ASPG\_DICCH) L-ASPARAGINASE [JZP-458]

### 2. Pharmacological class: Enzyme Replacement Therapy (asparaginase)

## Submissions Assessed

| Submission(s) Assessed                     | Document Date | Review Completed by:              |
|--------------------------------------------|---------------|-----------------------------------|
| STN 761179/0001- BLA pre-submission        | 12/09/2020    | OPMA Facilities                   |
| STN 761179/0002- Response to 12/04/2021 IR | 12/10/2020    | OPMA Facilities                   |
| STN 761179/0003- BLA Rolling Submission    | 12/18/2020    | Original Quality Submission       |
| STN 761179/0004- Response to 01/08/2021 IR | 01/13/2021    | OPMA Facilities                   |
| STN 761179/0007- Rolling Submission        | 02/19/2021    | OPQ                               |
| STN 761179/0011- Response to 02/16/2021 IR | 03/05/2021    | OPMA Microbiology                 |
| STN 761179/0015- Response to 03/09/2021 IR | 03/11/2021    | OPMA Facilities                   |
| STN 761179/0017- Proposed Labeling         | 03/15/2021    | OPQ                               |
| STN 761179/0019- Response to 03/12/2021 IR | 03/23/2021    | OBP Quality                       |
| STN 761179/0022 Response to 03/29/2021 IR  | 03/30/2021    | OPMA Facilities                   |
| STN 761179/0028- Response to 04/28/2021 IR | 05/07/2021    | OBP Quality and OPMA Microbiology |
| STN 761179/0032- Response to 05/12/2021 IR | 05/18/2021    | OPMA Microbiology                 |
| STN 761179/0038- Response to 05/25/2021 IR | 06/01/2021    | OPMA Microbiology                 |
| STN 761179/0040- Response to 06/01/2021 IR | 06/07/2021    | OBP Quality                       |
| STN 761179/0042- Response to 06/04/2021 IR | 06/08/2021    | OBP Quality and Immunogenicity    |
| STN 761179/0044- Response to 06/08/2021 IR | 06/11/2021    | OPMA Microbiology                 |
| STN 761179/0045- Response to 06/11/2021 IR | 06/08/2021    | OBP Quality and OPMA Facilities   |
| STN 761179/0048- Response to 06/15/2021 IR | 06/17/2021    | OBP Quality                       |
| STN 761179/0050- Response to 06/16/2021 IR | 06/21/2021    | OBP Quality                       |
| STN 761179/0051- Response to 06/16/2021 IR | 06/21/2021    | OBP Quality                       |
| STN 761179/0052- Response to 06/22/2021 IR | 06/23/2021    | OBP Quality and OPMA Microbiology |

## Quality Assessment Data Sheet

1. Legal Basis for Submission: 351(a)

2. Related/Supporting Documents:

A. DMFs:

| DMF #   | DMF Type | DMF Holder | Item referenced | Code <sup>1</sup> | Status <sup>2</sup> | Comments             |
|---------|----------|------------|-----------------|-------------------|---------------------|----------------------|
| (b) (4) | III      | (b) (4)    | (b) (4)         | 3                 | Adequate            | Provided in Seq 0003 |
|         | III      |            |                 | 3                 | Adequate            | Provided in Seq 0003 |
|         | V        |            |                 | 2                 | Adequate            | Provided in Seq 0003 |
|         | V        |            |                 | 3                 | Adequate            | Provided in Seq 0003 |

1. Action codes for DMF Table: 1- DMF Assessed; Other codes indicate why the DMF was not assessed, as follows:  
2- Assessed previously and no revision since last assessment; 3- Sufficient information in application; 4- Authority to reference not granted; 5- DMF not available; 6- Other (explain under "comments")

2. Action codes for Status column: Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application; therefore, the DMF did not need to be assessed).

B. Other documents: IND 129622

3. Consults: None

4. Environmental Assessment or Claim of Categorical Exclusion:

Jazz requests a categorical exclusion for RYLAZE under 21 CFR 25.31 (c) from preparation of an environmental assessment or an environmental impact statement.

## Executive Summary

### I. Recommendations:

#### A. Recommendation and Conclusion on Approvability:

Recommendation: Approval

The Office of Pharmaceutical Quality (OPQ), CDER, reviewed the product quality submission of STN 761179 for RYLAZE (asparaginase erwinia chrysanthemi (recombinant)-rywn, also known as JZP-458) manufactured by Jazz Pharmaceuticals Ireland Limited. The data submitted in this application are adequate to support the conclusion that the manufacture of RYLAZE is well-controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under conditions specified in the package insert.

#### B. Approval Action Letter Language:

- Manufacturing location:
  - Drug Substance (DS): (b) (4)
  - Drug Product (DP): (b) (4)
  - DP Vial Labeling and Secondary Packaging: (b) (4)
- Fill size and dosage form:
  - 10 mg solution in a 0.5 mL single-dose vial for intramuscular injection<sup>1</sup>
- Dating period:
  - Drug Product (DP): 24 months: 2-8 °C
  - Drug Substance (DS): (b) (4) °C
- For stability protocols:
  - We have approved the stability protocol in your license application for the purpose of extending the expiration dating of JZP-458 drug product under 21 CFR 601.12.
- Exempt from lot release:
  - RYLAZE is exempted from lot release per FR 95-29960.

#### C. Benefit/Risk Considerations:

The assessment of information provided in the application has concluded that the methodologies and processes used for JZP-458 DS and DP manufacturing, release and stability testing are robust and sufficiently controlled to lead to a product that is safe, pure and potent. The overall control strategy for JZP-458 manufacture incorporates control over raw materials, facilities and equipment, and the manufacturing process. The manufacturing control strategy coupled with in-process controls, release and stability testing ensures process consistency and product quality.

<sup>1</sup> The applicant proposes that the vials are filled to a target fill volume of (b) (4) mL to allow for a delivered volume of 0.5 mL.

Therefore, from a product quality perspective, this product is approvable for human use as described in the product labeling.

JZP-458 DS will be manufactured at (b) (4) and DP will be manufactured at (b) (4). Quality control testing will be performed mostly at (b) (4) and at other sites as summarized in section II.F of this document. A pre-licensure inspection (PLI) of the DS manufacturing facility (b) (4) was conducted during (b) (4) by CDER/OPQ. The final recommendation of voluntary action indicated (VAI) with an approval for BLA 761179 was made for (b) (4). A PLI for the DP manufacturing site (b) (4) was waived based on its inspection history. A recent OPMA pre-license inspection of (b) (4) was conducted on (b) (4) with coverage of the JZP-458 (b) (4), having a final outcome of VAI and a recommendation of approve for (b) (4). All facilities used for the manufacture and quality control testing of the product were found acceptable for the proposed operations (refer to sections II.F and II.G of this document).

The immunogenicity assays were validated for specificity, cut-point and titer determination, sensitivity, precision, selectivity, matrix interference, stability, and robustness. However, it was found that they are not sufficiently sensitive to detect anti-JZP-458 antibodies in presence of the expected level of JZP-458 in serum (refer to FDA OSIS Remote Record Review Recommendation- (b) (4)). This inadequate drug tolerance finding is not considered as an approvability issue given the acceptable safety profile and lack of actionable information based on ADA status.

Individual assessments for each discipline, (1) product quality of DS and DP [OBP], (2) immunogenicity assay validation [OBP], (3) microbiological control of DS and DP [OPMA/DBM], (4) facilities evaluation [OPMA/DBM], and (5) labeling [OBP] are located as separate documents in Panorama.

#### **D. Recommendation on Phase 4 (Post-Marketing) Commitments, Requirements, Agreements, and/or Risk Management Steps, if approvable:**

The following PMCs were proposed by OPMA and accepted by the Applicant:

**PMC-1:** To define and implement bioburden limits for routine reactivation of chromatography resins after extended storage. Report to be submitted on 12/31/2021.

**PMC-2:** To repeat the bacterial retention study (b) (4) Once (b) (4) validated, monitoring (b) (4) will be implemented during routine manufacturing. Report to be submitted on 09/30/2022.

**PMC-3:** To update the container closure integrity test method to include a 20-µm breached positive control. Report to be submitted on 09/30/2021.

The following PMCs were proposed by OBP and accepted by the Applicant:

PMC-4: To update the RP-UHPLC method validation to include impurities spiking study (e.g. pre-peaks and post-peaks are enriched to assess assay performance at different purity/impurity ratios). Final report submission on 06/30/2022.

The following PMCs were proposed by OBP and OCP and accepted by the Applicant:

PMC-5: Develop and validate a binding anti-drug antibody (ADA) assay with sufficient drug tolerance to be able to detect, confirm, and titer anti-RYLAZE binding antibodies in the presence of RYLAZE concentrations in clinical samples at the time of sampling. Final report submission on 02/2022.

PMC-6: Develop and validate a neutralizing ADA (NAb) assay with sufficient drug tolerance to detect neutralizing antibodies against RYLAZE in the presence of expected RYLAZE concentrations in clinical samples at the time of sampling. Final report submission on 09/2022.

PMC-7: Conduct a study examining quantitative recovery of anti-JZP458 antibodies from serum samples pretreated with Melon Gel Spin Plate Kit if immunogenicity data from an assay that uses the Melon Gel Spin Plate kit are used to support the license. Final report submission on 02/2022.

## II. Summary of Quality Assessments:

### A. CQA Identification, Risk and Lifecycle Knowledge Management

Table 1 is a summary of product-related critical quality attributes (CQA), intrinsic to the molecule, that are relevant to both DS and DP. The table includes the identification of the various attributes along with their risk management.

Table 1: Active Pharmaceutical Ingredient CQA Identification, Risk and Lifecycle Knowledge Management

| CQA (type)                  | Risk                                      | Origin                    | Control Strategy | Other   |
|-----------------------------|-------------------------------------------|---------------------------|------------------|---------|
| Identity                    | Bioactivity, PK, PD, safety, and efficacy | Intrinsic to the molecule | (b) (4)          |         |
| Primary Structure           | Efficacy                                  | Intrinsic to the molecule |                  |         |
| Higher Order Structure      | Efficacy                                  | Intrinsic to the molecule |                  |         |
| Specific Activity (Potency) | Bioactivity, PK, PD, safety, and efficacy | Intrinsic to the molecule |                  | (b) (4) |

|                                             |                                                          |                                                                                                           |         |                                  |
|---------------------------------------------|----------------------------------------------------------|-----------------------------------------------------------------------------------------------------------|---------|----------------------------------|
|                                             |                                                          |                                                                                                           |         | (b) (4)                          |
| Enzyme Kinetics (potency)                   | Bioactivity, PK, PD, safety, and efficacy                | Intrinsic to the molecule                                                                                 | (b) (4) |                                  |
| Main Peak (purity)                          | Bioactivity, PK, PD, efficacy and safety                 | May change during manufacturing process and storage                                                       |         |                                  |
| Main Peak (purity)                          | Bioactivity, PK, PD, efficacy and safety                 | May change during manufacturing process and storage                                                       |         |                                  |
| Main Peak (purity)                          | Bioactivity, PK, PD, efficacy and safety                 | May change during manufacturing process and storage                                                       |         |                                  |
| Oxidized Species (Product-related impurity) | Bioactivity, PK, PD, immunogenicity, and efficacy        | Intrinsic to the molecule, and the relative abundance can change during manufacturing process and storage |         | Stability-indicating.<br>(b) (4) |
| HMW Species (product-related impurity)      | Bioactivity, PK, PD, immunogenicity, safety and efficacy | Can be introduced during manufacturing process, may increase during storage                               |         | Stability-indicating.<br>(b) (4) |
| LMW Species (product-related impurity)      | Bioactivity, PK, PD, efficacy and safety                 | Can be introduced during manufacturing process, may increase during                                       |         | Stability-indicating.<br>(b) (4) |

|                                                                              |          |                                                                                                           |         |                                  |
|------------------------------------------------------------------------------|----------|-----------------------------------------------------------------------------------------------------------|---------|----------------------------------|
|                                                                              |          | storage                                                                                                   |         | (b) (4)                          |
| Acidic and Basic Species<br>(product-related variants, charge heterogeneity) | Efficacy | Intrinsic to the molecule, and the relative abundance can change during manufacturing process and storage | (b) (4) | Stability-indicating.<br>(b) (4) |

**B. Drug Substance [asparaginase erwinia chrysanthemi (recombinant)-rywn, JZP-458]  
Quality Summary**

Table 2 provides a summary of the identification, risk, and lifecycle knowledge management for drug substance CQAs that derive from the drug substance manufacturing process and general drug substance attributes, including process-related impurities.

Table 2: Drug Substance CQA Identification, Risk and Lifecycle Knowledge Management

| CQA (type)                                                         | Risk                                                                                                      | Origin                                                                        | Control Strategy | Other                                                                                                  |  |
|--------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------|------------------|--------------------------------------------------------------------------------------------------------|--|
| Appearance: color and clarity<br><br>(general)                     | Safety and Immunogenicity                                                                                 | Manufacturing process, formulation                                            | (b) (4)          |                                                                                                        |  |
| pH<br><br>(general)                                                | Safety                                                                                                    | Manufacturing process, formulation                                            |                  |                                                                                                        |  |
| Protein Concentration<br><br>(strength)                            | Bioactivity, PK, PD, and efficacy                                                                         | manufacturing process                                                         |                  |                                                                                                        |  |
| Host cell DNA<br><br>(Process-related impurities)                  | safety                                                                                                    | Cell culture                                                                  |                  | The release specification is (b) (4) (under the WHO recommended safety limit of 10 ng/dose)            |  |
| Residual HCP<br><br>(Process-related impurities)                   | Safety (immunogenicity)                                                                                   | Cell culture                                                                  |                  | The release specification is (b) (4) pg/mg                                                             |  |
| (b) (4)                                                            | Safety                                                                                                    | (b) (4)                                                                       |                  | These process-related impurities were below the limit of detection (LOD) and permitted daily exposure. |  |
| (Process-related impurities)                                       |                                                                                                           |                                                                               |                  |                                                                                                        |  |
| Bioburden<br><br>(Process-related impurities, adventitious agents) | Safety, purity, and efficacy (degradation or modification of the product by contaminating microorganisms) | Can be introduced from raw materials and throughout the manufacturing process | (b) (4)          | The release specification is (b) (4) for TAMC and TYMC                                                 |  |
| Endotoxin<br><br>(Process-related impurities, adventitious agents) | Safety, purity                                                                                            |                                                                               |                  | The release specification is (b) (4) EU/mg                                                             |  |

- Description: JZP-458 is a recombinant crisantaspase (the native asparaginase *Erwinia chrysanthemi*) produced in *Pseudomonas fluorescens*. It is a tetrameric 140 kDa enzyme consisting of four 35 kDa subunits formed by noncovalent/non-disulfide interactions.
- Mechanism of Action (MoA): JZP-458 catalyzes L-asparagine to L-aspartic acid and ammonia. The mechanism of action of JZP-458 is based on the killing of leukemic cells due to depletion of plasma asparagine. Leukemic cells with low expression of asparagine synthetase have a reduced ability to synthesize asparagine, and therefore depend on an exogenous source of asparagine for survival.

- **Potency Assay:** The biological activity of JZP-458 is determined by a colorimetric assay using the Nessler reagent which measures the amount of ammonia released during hydrolysis of L-asparagine by JZP-458. The ammonia released interacts with Nessler reagent, a solution of potassium tetraiodomercurate (II) ( $K_2[HgI_4]$ ) in concentrated potassium hydroxide (KOH), to form water soluble yellow complex  $HgO.Hg(NH_2)$  that absorb light at 450 nm. The activity of JZP-458 is expressed in units, defined as the amount of enzyme that catalyzes the conversion of  $1\mu\text{mol}$  of L-asparagine per reaction minute, per mg of protein. A normalization factor, established RS value (average activity stated in the respective control chart) divided by determined RS value (measured RM activity in the setup), is used to reduce routine assay variability. Appropriate system suitability acceptance criteria are in place for measured RS value in each setup to avoid inaccurate sample values.
- **Reference Materials:** Consistent with ICH Q6B, a two-tiered reference standard (RS) system has been established for control of commercial RYLAZE. (b) (4)

[Redacted text block]

[Redacted text block]

C. Drug Product [asparaginase erwinia chrysanthemi (recombinant)-rywn, JZP-458]  
Quality Summary:

Table 3 provides a summary of the identification, risk, and lifecycle knowledge management for drug product CQAs that derive from the drug product manufacturing process and general drug product attributes.

Table 3: Drug Product CQA Identification, Risk, and Lifecycle Management

| CQA (type)                                      | Risk                                                                                                                                                                      | Origin                                                                                                                        | Control Strategy |
|-------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------|------------------|
| Sterility<br>(contaminant)                      | Safety, purity, and efficacy<br>(degradation or modification<br>of the product by<br>contaminating<br>microorganisms)                                                     | Contamination may be<br>introduced throughout<br>the DP manufacturing<br>process or by container<br>closure integrity failure | (b) (4)          |
| Endotoxin<br>(contaminant)                      | Safety and purity                                                                                                                                                         | DP manufacturing<br>process and by raw<br>materials                                                                           |                  |
| Container closure<br>integrity<br>(contaminant) | Safety (Failure in closure<br>integrity may lead to<br>contamination through a loss<br>of sterility) or<br>evaporation/leakage<br>(impacting concentration or<br>content) | Breach during the<br>manufacturing process<br><br>May be impacted by<br>storage conditions                                    |                  |
| Color<br>(Appearance)                           | Safety                                                                                                                                                                    | DP Manufacturing<br>process, formulation                                                                                      |                  |
| Clarity<br>(Appearance)                         | Safety                                                                                                                                                                    | DP Manufacturing<br>process, formulation                                                                                      |                  |
| Visible Particles<br>(Appearance)               | Safety                                                                                                                                                                    | DP manufacturing<br>process, CCS, and<br>product                                                                              |                  |
| Subvisible particles<br>(general)               | Safety                                                                                                                                                                    | DP manufacturing<br>process, CCS, and<br>product                                                                              |                  |
| pH<br>(general)                                 | Safety                                                                                                                                                                    | Formulation                                                                                                                   |                  |
| Osmolality<br>(general)                         | Patient discomfort                                                                                                                                                        | Formulation                                                                                                                   |                  |

|                                     |                     |                                                                    |         |
|-------------------------------------|---------------------|--------------------------------------------------------------------|---------|
| Extractable Volume<br>(general)     | Inaccurate dosing   | DP manufacturing<br>process, CCS                                   | (b) (4) |
| Protein content<br>(quantity)       | Efficacy            | DP manufacturing<br>process, formulation                           |         |
| PS80 concentration<br>(composition) | Safety and Efficacy | Formulation component,<br>May be impacted by<br>storage conditions |         |

- **Potency and Strength:** 10 mg JZP-458 in a 0.5 mL vial. The vials are filled to a target fill volume of (b) (4) mL to allow for a delivered volume of 0.5 mL. The overfill of (b) (4) mL is slightly above USP <1151> recommended allowable overfill of 0.12 mL for 0.5 mL target volume, which is acceptable because this difference unlikely to lead to misuse or medication error. The potency of JZP-458 DP is determined using the same enzyme activity assay used for release and stability testing of DS.
- **Summary of Product Design:** The DP is filled in glass vials as sterile solution for intramuscular injection. The DP is withdrawn from vials using disposable sterile syringe(s) and administered immediately. Multiple vials may be pooled for a full dose.
- **List of Excipients:** (b) (4) trehalose, (b) (4) sodium chloride, (b) (4) sodium phosphate buffer, (b) (4) polysorbate 80, pH 7.0, and water for injection (q.s. 0.5 mL).
- **Reference Materials:** Same as JZP-458 DS reference standards.
- **Manufacturing process summary:**

(b) (4)

- **List of co-package components, if applicable:** None.

**D. Novel Approaches/Precedents:** None.

**E. Any Special Product Quality Labeling Recommendations:** None.

**F. Establishment Information:**

| Overall Recommendation: Approval                                                                                                                                                                                                             |                                                                                                      |            |                                                   |                                                                                                                                                                                                 |                                                         |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|------------|---------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------|
| Function                                                                                                                                                                                                                                     | Site Information                                                                                     | FEI Number | Preliminary Assessment                            | Inspectional Observations                                                                                                                                                                       | Final Recommendation                                    |
| - DS manufacture<br>- DS and DP release and stability testing (appearance, pH, osmolality, protein concentration, PS80 content, peptide mapping, RP-UHPLC, SE-UHPLC, rCE-SDS, CIE-XUHPLC, and specific activity)<br>- Storage of MCB and WCB | (b) (4)                                                                                              | (b) (4)    | PLI Required                                      | PLI: 2-item FDA Form 483*                                                                                                                                                                       | Approve based on PLI                                    |
| - DP manufacture<br>- DP release and stability testing (particulate matter, extractable volume, endotoxin, sterility, and identity by SDS-PAGE)<br>- Secondary Packaging and labeling                                                        |                                                                                                      |            | PLI Waived based on history                       | Last inspection was completed on (b) (4), which was an OPMA PLI for the (b) (4). A Form 483 was issued. The compliance review was acceptable and had a recommendation for the inspected BLA DP. | Approve based on compliance waiver granted by OPMA/OBP. |
| - DS and DP release and stability testing (Enzyme kinetics $K_M/K_{cat}$ )                                                                                                                                                                   |                                                                                                      |            | Facility was found compliant based on file review | Last inspection was completed (b) (4) and was a surveillance inspection. No Form 483 was issued.                                                                                                | Approve based on compliance history                     |
| - Release of DS and DP                                                                                                                                                                                                                       | Jazz Pharmaceuticals Ireland Limited, Fifth Floor, Waterloo Exchange Waterloo Road, Dublin 4 Ireland | 3012774443 | No Evaluation Necessary                           | Last inspection was completed (b) (4). No deficiencies were noted.                                                                                                                              | No Evaluation Necessary                                 |
| - Production and initial storage of MCB and WCB                                                                                                                                                                                              | (b) (4)                                                                                              |            | No Evaluation Necessary                           | Last inspection was completed (b) (4) and was a surveillance inspection. No Form 483 was issued.                                                                                                | No Evaluation Necessary                                 |

|                                                             |         |                                                   |                                                                                                  |                                     |
|-------------------------------------------------------------|---------|---------------------------------------------------|--------------------------------------------------------------------------------------------------|-------------------------------------|
| - Storage of MCB and WCB                                    | (b) (4) | No Evaluation Necessary                           | N/A                                                                                              | No Evaluation Necessary             |
| -DP stability testing (Container-Closure Integrity Testing) | (b) (4) | Facility was found compliant based on file review | Last inspection was completed (b) (4) and was a surveillance inspection. No Form 483 was issued. | Approve based on compliance history |

\*2-item FDA Form 483:

- 1) Failure to assure that personnel have the necessary training in sample handling operations which they perform. Specifically, handling of samples for testing of 1062 in-process controls, drug substance and drug product does not include appropriate analyst training to ensure conformance to appropriate standards of quality and purity.
- 2) Change control regarding test method documents updates is not implemented in a timely manner to avoid reoccurring deviations

#### G. Facilities: No approvability issues.

Adequate descriptions of the facilities, equipment, environmental controls, cleaning and contamination control strategy were provided for (b) (4) proposed for Drug Substance (DS) and Drug Product (DP) manufacture, respectively. All proposed manufacturing and testing facilities are acceptable based on their current CGMP compliance status and recent relevant inspectional coverage.

#### H. Lifecycle Knowledge Management:

##### a. Drug Substance:

##### i. Protocols approved:

1. MCB and WCB long term stability monitoring protocols (3.2.S.2.3)
2. Concurrent release protocol for chromatography resin lifetime (3.2.S.2.5)
3. Requalification of reference standards protocol (3.2.S.5)
4. Qualification of new working reference standards protocol (3.2.S.5)
5. Post-approval annual stability protocol (3.2.S.7.2)

##### ii. Outstanding assessment issues/residual risk:

1. Upon agreement with the Agency (refer to Type C meeting minutes, IND 129622 SN 0041), the following data will be submitted in post-approval annual report:
  - a. The hold stability data for DS process solutions and media.
  - b. The mixing validation data for media, buffers, and solutions used in DS manufacturing.
  - c. The current HCP method uses the commercial Cygnus kit. Jazz committed to develop and validate an in-house HCP assay specifically for JZP-458 and submit the information and data for this new assay.
2. See PMC 1-4 in section I.D above.

##### iii. Future inspection points to consider:

1. Verify whether the measured WRS specific activity in assays (known as setups at (b) (4)) are within the limits specified in the WRS specific activity control chart.

2. Check if the investigation of deviation [REDACTED] (b) (4)  
[REDACTED] is present  
in other commercial DS and DP stability samples.

**b. Drug Product**

**i. Protocols approved:**

1. Post-approval annual stability protocol (3.2.P.8.2)

**ii. Outstanding assessment issues/residual risk:** None.

**iii. Future inspection points to consider:** None.

**c. Immunogenicity Assay Validation**

**i. Protocols approved:** N/A

**ii. Outstanding assessment issues/residual risk:**

1. There was drug tolerance issue for the binding ADA assay (refer to OSIS RRR Observation #1). A PMC is agreed by the Applicant to develop and validate a binding ADA assay with sufficient drug tolerance to detect, confirm and titer anti-RYLAZE (JZP-458) binding antibodies in the presence of expected RYLAZE concentrations in clinical samples at the time of sampling.
2. Because the binding ADA assay has drug tolerance issue, the NAb assay may also have drug tolerance issue, so a PMC is agreed by the Applicant to develop and validate a NAb assay with sufficient drug tolerance to detect neutralizing antibodies against RYLAZE in the presence of expected RYLAZE concentrations in clinical samples at the time of sampling
3. The use of Melon Gel Spin Plate Kit increases sensitivity of the neutralizing ADA (NAb) assay, but the Applicant did not provide direct evidence for no ADA loss during this pretreatment step. A PMC is agreed by the Applicant to conduct a study examining quantitative recovery of anti-JZP458 antibodies from serum samples pretreated with Melon Gel Spin Plate Kit if immunogenicity data from an assay that uses the Melon Gel Spin Plate kit are used to support the license.

**iii. Future inspection points to consider:** Refer to OSIS RRR Recommendation- [REDACTED] (b) (4)

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**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.**  
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/s/  
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ZHENZHEN LIU  
06/28/2021 05:06:48 PM

SUSAN L KIRSHNER  
06/28/2021 06:50:27 PM

## PRODUCT QUALITY MICROBIOLOGY ASSESSMENT

|                             |                                                                                                                                                             |
|-----------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Application ID</b>       | BLA 761179                                                                                                                                                  |
| <b>Submission Type</b>      | Original BLA                                                                                                                                                |
| <b>Drug Product Name</b>    | Asparaginase erwinia chrysanthemi (recombinant) (Rylaze)                                                                                                    |
| <b>Strengths</b>            | 20 mg/mL                                                                                                                                                    |
| <b>Dosage Form</b>          | Sterile solution for injection                                                                                                                              |
| <b>Administration Route</b> | IM injection                                                                                                                                                |
| <b>Indication</b>           | Treatment of ALL and LBL in adult and pediatric patients who have developed hypersensitivity or silent inactivation to <i>E. coli</i> -derived asparaginase |
| <b>Applicant Name</b>       | Jazz Pharmaceuticals Ireland Limited                                                                                                                        |
| <b>US License Number</b>    | 2167                                                                                                                                                        |
| <b>Application Type</b>     | 351 (a)                                                                                                                                                     |
| <b>Primary Reviewer</b>     | Reyes Candau-Chacon, PhD (Microbiology)                                                                                                                     |
| <b>Secondary Reviewer</b>   | Virginia Carroll, PhD                                                                                                                                       |
| <b>Goal Date</b>            | 4/30/2022                                                                                                                                                   |

### Recommendation for Approvability:

- This BLA was reviewed from a product quality microbiology perspective and sterility assurance perspective and is recommended for approval with the following post-marketing commitments:
  1. To define and implement bioburden limits for routine reactivation of chromatography resins after extended storage. Report to be provided by December 31, 2021.
  2. To repeat the bacterial retention study (b) (4) (b) (4) Once (b) (4) validated, monitoring (b) (4) will be implemented during routine manufacturing. Report and implementation dates to be provided by September 30, 2022.
  3. To update the container closure integrity test method to include a 20-µm breached positive control. Report to be provided by December 31, 2021.
- Product quality aspects not related to microbial control and facilities should be reviewed by OBP.

### Summary Basis of Recommendation (DS):

Overall, the process is under adequate microbial control. Microbial quality is controlled (b) (4)

**Drug Substance CQA Process Risk Identification and Lifecycle Knowledge Management:**

| CQA (type) | Risk                                                                                                     | Origin                               | Control Strategy |
|------------|----------------------------------------------------------------------------------------------------------|--------------------------------------|------------------|
| Endotoxin  | Safety, Purity                                                                                           | Raw materials, manufacturing process | (b) (4)          |
| Bioburden  | Safety, Purity and Efficacy due to degradation or modification of the product by microbial contamination | Manufacturing process                |                  |

**Summary Basis of Recommendation (DP):**

|         |  |  |  |
|---------|--|--|--|
| (b) (4) |  |  |  |
|---------|--|--|--|

**Drug Product CQA Process Risk Identification and Lifecycle Knowledge Management:**

| CQA (type)                                        | Risk                                                                                                     | Origin                                                            | Control Strategy |
|---------------------------------------------------|----------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------|------------------|
| Sterility (Contaminant)                           | Safety, Purity and Efficacy due to degradation or modification of the product by microbial contamination | Manufacturing process, failure of the container closure integrity | (b) (4)          |
| Endotoxin (Contaminant)                           | Safety, Purity                                                                                           | Raw materials, manufacturing process                              |                  |
| Container closure integrity (Sterility assurance) | Safety (Sterility assurance)                                                                             | Breach during manufacture or storage                              |                  |

**List Submissions being assessed (Table):**

| Amendment # | Document description                     | Date Received     |
|-------------|------------------------------------------|-------------------|
| 0003        | Module 3 submission                      | December 18, 2020 |
| 0011        | Response to IR sent on February 16, 2021 | March 5, 2021     |
| 0028        | Response to IR sent on April 28, 2021    | May 7, 2021       |
| 0032        | Response to IR sent on May 12, 2021      | May 18, 2021      |

|      |                                                    |               |
|------|----------------------------------------------------|---------------|
| 0038 | Response to IR sent on May 25, 2021                | June 1, 2021  |
| 0044 | Response to IR sent on June 8, 2021                | June 11, 2021 |
| 0049 | BLA updates as per information provided in the IRs | June 21, 2021 |
| 0052 | PMC language and reporting dates                   | June 22, 2021 |
| 0054 | BLA update of Section S.2.4                        | June 23, 2021 |

**List of DMFs (Table):**

| DMF #   | Description | Finding  | Document Reference | Review date |
|---------|-------------|----------|--------------------|-------------|
| (b) (4) | (b) (4)     | Adequate | (b) (4)            | 4/2/2019    |

*Reviewer's comment: The DMF review covers* (b) (4)

## MODULE 1

### 1.14 LABELING

The dosage form is a 10 mg/0.5 mL solution in a single-dose vial. The recommended dose of asparaginase erwinia chrysanthemi (recombinant) is 25 mg/m<sup>2</sup> on Monday and Wednesday and 50 mg/m<sup>2</sup> on Friday for a total of six doses every two weeks. The product is administered intramuscularly. Unused product from a partial-used vial is to be discarded.

*Reviewer's comment: The product is provided as a solution in a single-use vial that is discarded after opening if not used. Administration is intramuscular. There are no concerns related to sterility assurance or endotoxin levels.*

## MODULE 3.2.S

### S.1 General Information

Recombinant crisantaspase (RC-P, JZP-458) is expressed in *Pseudomonas fluorescens*. JZP-458 is a tetramer enzyme with 4 identical polypeptide subunits. Each subunit has a molecular weight of 35 kDa. JZP-458 is an Asparaginase enzyme that hydrolyzes L-asparagine to L-aspartic acid and ammonia.

### S.2 Manufacture

#### S.2.1 Manufacturer(s)

The following facilities are used for the manufacture and microbial release testing of JZP-458 drug substance:

(b) (4)



Reyes  
Candau-Chacon

Digitally signed by Reyes Candau-Chacon  
Date: 6/28/2021 02:35:48PM  
GUID: 508da7160002977f7ca389c8f849b707



Virginia  
Carroll

Digitally signed by Virginia Carroll  
Date: 6/28/2021 02:40:49PM  
GUID: 5898c0190049a524b6af8a93d389a1c0

**351(a) BLA IMMUNOGENICITY ASSESSMENT**

|                                         |                                                                                                                                                                      |
|-----------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Application Type</b>                 | BLA (RTOR)                                                                                                                                                           |
| <b>Application Number</b>               | 761179                                                                                                                                                               |
| <b>Submit Date</b>                      | 12/19/2019                                                                                                                                                           |
| <b>Received Date</b>                    | 04/30/2021                                                                                                                                                           |
| <b>Review Date</b>                      | 06/25/2021                                                                                                                                                           |
| <b>PDUFA Goal Date</b>                  | 04/30/2022                                                                                                                                                           |
| <b>Division/Office</b>                  | DHMI/OOD/OND                                                                                                                                                         |
| <b>Product Code Name</b>                | JZP-458                                                                                                                                                              |
| <b>Non-proprietary Name</b>             | asparaginase erwinia chrysanthemi (recombinant)                                                                                                                      |
| <b>Proposed Proprietary Name</b>        | Rylaze                                                                                                                                                               |
| <b>Pharmacologic Class</b>              | Enzyme Replacement Therapy (Asparaginase)                                                                                                                            |
| <b>Applicant</b>                        | Jazz Pharmaceuticals Ireland Limited                                                                                                                                 |
| <b>Applicant Proposed Indication(s)</b> | Treatment of patients with acute lymphoblastic leukemia (ALL)/lymphoblastic lymphoma (LBL) who have developed hypersensitivity to <i>E.coli</i> derived asparaginase |
| <b>Recommended Regulatory Action</b>    | Approval                                                                                                                                                             |

## Immunogenicity Reviewers

|                              |                                             |
|------------------------------|---------------------------------------------|
| <b>Primary Reviewer(s)</b>   | Mekonnen Lemma Dechassa, Ph.D., OBP/DBRRIII |
| <b>Secondary Reviewer(s)</b> | Zhenzhen Liu , Ph.D., OBP/DBRRIII           |
| <b>Tertiary Reviewer</b>     | Susan Kirshner, Ph.D., OBP/DBRRIII          |

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## 1. Summary Basis of Recommendation/Executive Summary

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### 1.1 Immunogenicity Executive Summary and Recommendation

JZP-458 (asparaginase *erwinia chrysanthemi* (recombinant)) is a recombinant L-asparaginase from *Dickeya dadantii* (previously known as *Erwinia chrysanthemi*) expressed in *Pseudomonas fluorescens*. The primary structure of JZP-458 is the same as *Dickeya dadantii*-derived L-asparaginase, Erwinaze. JZP-458 is a tetrameric 140 kDa enzyme consisting of four 35 kDa subunits. JZP-458 catalyzes L-asparagine to L-aspartic acid and ammonia.

JZP-458 is a component of multi-agent chemotherapy for acute lymphoblastic leukemia (ALL)/Lymphoblastic Lymphoma (LBL) for patients that developed hypersensitivity to *E. coli* derived L-asparaginase. Leukemia cells are deficient in asparagine synthesis and dependent on circulating asparagine for survival while normal cells can synthesize asparagine and are less dependent on circulating asparagine. JZP-458 depletes circulating asparagine and depriving leukemia cells of asparagine amino acid, which impacts their metabolism and survival.

In the phase 2/3 study JZP458-201, 6 doses of JZP-458 were substituted for each dose of a long-acting *E. coli*-derived L-asparaginase at any point during the treatment course of pediatric and adult patients with ALL/LBL. The 6 doses of JZP-458 (defined as one course) is given over two consecutive weeks (3 doses per week, e.g., on Monday, Wednesday, and Friday (MWF)). The number of JZP-458 treatment courses depend on the number of the remaining doses of long-acting *E. coli*-derived asparaginase. The interval between JZP-458 courses vary from back-to-back to several weeks' interval between JZP-458 treatment courses.

Because of the fast track development program of JZP-458, BLA 761179 has limited immunogenicity data derived from one clinical study JZP458-201. JZP458-201 consists of Part A (IM administration) and Part B (IV administration). The immunogenicity assessment in the BLA covered only Part A: 33 patients from IM Cohort 1a (25 mg/m<sup>2</sup> administered MWF) and 53 patients from IM Cohort b (37.5 mg/m<sup>2</sup> administered MWF) at data cut-off October 14, 2020. A total of 140 and 147 samples were collected from participants in IM Cohort 1a and IM Cohort 1b, respectively. Antidrug antibody (ADA) data were available from 1 to 14 courses from 33 participants in Cohort 1a, and 1 to 6 courses from 53 participants in Cohort 1b. The Applicant plans to submit the final analysis late in the BLA review cycle.

For immunogenicity assessment, the Applicant (Jazz) used a multi-tiered testing approach including screening, confirmatory, titration, and neutralization assays to detect binding and neutralizing anti-drug antibodies (ADA) against JZP-458 in the patient serum samples. Jazz contracted (b) (4) to develop and validate the MesoScale Discovery (MSD) platform electrochemiluminescence (ECL) bridging ELISA used for ADA testing and the L-asparaginase enzymatic inhibition assay for neutralizing ADA (NAb) detection.

The preliminary immunogenicity assessment shows that there was a high ADA rate toward JZP-458 (27/86, 31%). Two of the 27 JZP-458 treatment patients positive for ADA had reduced serum asparaginase activity (SAA) without having NAb activity. Three of the 27 ADA positive patients had NAb but the SAA level in these patients was not impacted.

The following issues were identified by FDA/OTS/OSIS colleagues when they performed remote record review of these assays and PK/PD assays:

- The ADA/NAb assays had inadequate drug tolerance.
- The ADA and the JZP-458 are interfering with detection of each other: JZP-458 interferes with the measurement of ADA, and the ADA interferes with the measurement of JZP-458, which impact the interpretation of the clinical immunogenicity data.

In addition, the assessment of method validation reports identified that the Melon Spin method used for mitigation of drug tolerance in NAb analysis was not evaluated for its impact on recovery of ADA against JZP-458. These findings are not approvability issues given the observed acceptable safety profile and lack of actionable information based on ADA status. A PMR (See Clinical Pharmacology Review memo by Dr. Lauren Price) and 3 PMCs (see PMCs below) are under discussion with the Applicant to address these issues as of the time of finalizing this memo. Refer to the OPQ Executive Summary Review Memo wrote by Dr. Zhenzhen Liu for the final language of these PMCs.

## 1.2 Deficiencies and Other Recommended Comments to Applicant

No deficiencies.

## 2. Review

| Document Reviewed | Submission Date | Review Content                              |
|-------------------|-----------------|---------------------------------------------|
| BLA 761179 SN0005 | 01/28/2021      | ADA assay validation reports                |
| BLA 761179 SN0025 | 04/30/2021      | Integrated summary of immunogenicity report |
| BLA 761179 SN0042 | 06/08/2021      | IR response                                 |

### 2.1 Background Immunogenicity Information

The immunogenicity assessment that was conducted in Study JZP458-201 includes pediatric and adult participants with ALL/LBL administered with repeated IM doses of JZP-458. Patients treated with native *Erwinia chrysanthemi*-derived asparaginase (Erwinaze) have been shown to develop ADA and hypersensitivity reactions (see *Erwinaze PI*). Based on the structure and physiochemical similarity of JZP-458 to native *Erwinia chrysanthemi*-derived asparaginase, ADA and hypersensitivity are expected in patients treated with JZP-458.

A multi-tiered approach was used to measure ADA and neutralizing antibody (NAb) to evaluate immunogenicity of JZP-458 in clinical Study JZP458-201. Jazz developed ADA assays for detection, confirmation, and titer determination based on electrochemiluminescent immunoassay (ECLIA) method. The NAb assay used is based on serum asparaginase activity assay.

### 2.2 Validation of the Anti-Drug Antibody Assay

An ECLIA method for detection, confirmation, and titer determination of anti-JZP-458 antibodies in human serum was validated by (b) (4) who also conducted testing of the clinical samples. A signed validation report (No. 2018-458-042) dated January 13, 2020 for ADA assay is submitted in section 5.3.1.4. Forty-one analytical runs were performed, and the validation study results demonstrated that the method is suitable for ADA detection, confirmation, and titer determination.

#### 2.2.1 Method Principle

The assay is based on an ECLIA platform using a 96-well Meso Scale Discovery (MSD) microtiter plate coated with streptavidin. The positive controls (PCs) consisted of an anti-Erwinase (*Erwinia chrysanthemi*-derived asparaginase) antibody (rabbit IgG) spiked in human serum at two concentrations: low positive control (LPC) and high positive control (HPC). The negative control (NC) consisted of pooled human serum.

The assay performed is a typical ECLIA based on streptavidin-coated MSD plate. Briefly, the streptavidin-coated MSD plate was blocked by incubating for 1-3 hours at room temperature (RT). The PCs (LPC and HPC) and NC were diluted 5-fold in phosphate buffer saline (PBS) and the diluted PCs and NC were then diluted 2-fold in the master mix consisting of biotinylated JZP-458 and sulfo-tagged JZP-458 in dilution plate, followed by incubation for 2 hours at RT. After washing the streptavidin-coated MSD plate, the PCs and NC were loaded onto blocked streptavidin-coated MSD plate and incubated for an hour at RT. After washing the plate, MSD read buffer was added to the wells of the plate and the plate was read using a MSD Sector S 600 reader. In principle, the biotinylated JZP-458 (RC-P) and sulfo-tagged JZP-458 form a complex through ADA against JZP-458. The complex is captured on streptavidin coated plate and resulting ECL signal that is proportional to the amount of ADA present in the human serum.

Analysis was conducted in three tiers: an initial screening analysis for ADA positive samples was followed by a confirmatory analysis and then a titer analysis. Samples with ECL response above the screening plate-specific screening cut point (PSCP) are considered positive for ADA. PSCP is set based on the median ECL response of the NC corrected with a factor established during assay validation. The confirmatory assay is conducted by testing controls and samples in the absence and presence of 8.00 µg/mL JZP-458. Samples confirmed positive for ADA when %inhibition (%INH) is above a fixed confirmatory cut point (CCP) established during assay validation.

## 2.2.2 Validation Exercises

**Table 2.1: Validation Results and Reviewer Assessment for ADA Assays Used in Study JZP458-201**

| Validation Parameter  | Validation Report: 00350526                                                                                                                                                                                                                                                                                                                                                                                                               | Reviewer Comment                                                                                   |
|-----------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------|
| Contract Research Org | (b) (4)                                                                                                                                                                                                                                                                                                                                                                                                                                   | (b) (4)                                                                                            |
|                       |                                                                                                                                                                                                                                                                                                                                                                                                                                           | <i>Clinical samples were analyzed at this site</i>                                                 |
| Assay principle       | MSD-based ECL assay: serum samples with ADA are incubated with master mix containing biotin-JZP-458 and Sulfo-tagged JZP-458 and added onto streptavidin-coated MSD plates. The ADA against JZP-458 forms a bridge between biotin-JZP-458 and Sulfo-tagged JZP-458 to allow the binding of the formed complex to the streptavidin-coated plate. The resulting ECL signal is proportional to the amount of ADA present in the human serum. | <i>This is a standard bridging immunoassay to detect ADAs in human serum, which is acceptable.</i> |

|                                                            |                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Positive control (PC)                                      | Monospecific Anti-Erwinaze® Rabbit IgG<br>Lot No.: EUSAERWIGG1106001043012<br>Storage: -60°C to -80°C                                                                                                                                                                                                           | <i>The assay used an in-house positive control. Use of in-house controls for 351(a) products is a standard industry practice. The monospecific Anti-Erwinaze® Rabbit IgG was used throughout the validation process. Since Erwinaze and JZP-458 share the same biochemical structure, anti-Erwinaze IgG is acceptable to be used as the PC for anti-JZP-458 antibodies detection assay because the anti-Erwinaze IgG can bind to JZP-458 and form positive signals in the ECL assay.</i>                                                            |
| Reference standard (RS)                                    | JZP-458 (RC-P):<br>Lot No.: CMC-M-0002 (GMP-2)<br>Storage: -10°C to -30°C<br>Expiration/retest date: April 19, 2020                                                                                                                                                                                             | <i>JZP-458 lot CMC-M-002 was used throughout the validation process.</i>                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| Positive control (PC) Dose Curve and Prozone (Hook Effect) | ECL values increase with increasing concentration and plateau at the higher PC concentrations (4500-36,900 ng/mL). Hook effect was detected at antibody concentrations above 36,900 ng/mL, at concentration of positive control where ECL signal starts decreasing.                                             | <i>The Applicant states that “the sample response in clinical samples will be monitored to assure that samples are not diluted into the prozone of the assay”. This is acceptable.</i>                                                                                                                                                                                                                                                                                                                                                              |
| LPC                                                        | Screening LPC (sLPC)= 0.6 ng/mL<br>Confirmatory LPC (cLPC)= 0.8 ng/mL<br>sLPC and cLPC were calculated from sensitivity results as follow:<br><ul style="list-style-type: none"> <li>- sLPC = Mean PC at PSCP + (t0.01,df × SD)=0.4ng/mL</li> <li>- cLPC = Mean PC at CCP + (t0.01,df × SD)=0.6ng/mL</li> </ul> | <i>A separate LPC was required for the confirmatory assay as it was less sensitive than the screening assay.<br/><br/>The initial calculated sLPC and cLPC were 0.40 ng/mL and 0.60 ng/mL, respectively. These levels did not consistently meet routine run acceptance criteria (the cause was not identified). The sLPC and cLPC were prepared at 0.60 ng/mL and 0.8 ng/mL, which were subsequently used for method validation. This is acceptable because they are still way below the recommended sensitivity of 100 ng/mL for screening and</i> |

|                                                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                                                                                                                           |
|--------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | <i>confirmatory assay in the 2019 FDA guidance.</i>                                                                                                                                                                                       |
| HPC                                                                                  | 250 ng/mL                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | <i>This is acceptable because the ECL values for the HPC are proportionally higher than those for the LPCs and the HPC is under the prozone level.</i>                                                                                    |
| Matrix and NC                                                                        | Human serum                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | <i>The use of pooled human serum as the matrix control is acceptable as it is a standard industry practice.</i>                                                                                                                           |
| MRD                                                                                  | 1/10                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | <i>Acceptable.</i>                                                                                                                                                                                                                        |
| NC system suitability range                                                          | <p>ECL response: <math>\leq 95</math></p> <p>At least 2/3 duplicate sets of NC ECL <math>\leq 95</math></p> <p>Precision between duplicate wells <math>\leq 20\%CV</math></p> <p>The upper limit of NC was determined using inter-assay median response, as follow:</p> <p>Upper Limit = Median NC + <math>t_{0.01,df} \times SD = 95</math> ECL, with 1% failure rate</p> <p>NC was used to adjust the SCP and TCP on each plate to determine the PSCP and PTSCP, respectively.</p> | <i>The NC determined during validation study was also used to adjust plate cut points during ADA testing of clinical samples.</i>                                                                                                         |
| LPC system suitability range                                                         | <p>sLPC Signal-to-Noise (S/N) ratio <math>\geq 1.66</math></p> <p>cLPC S/N ratio <math>\geq 1.90</math></p> <p>lower Limit = mean (PC/Median NC) - <math>t_{0.01,df} \times SD</math>, with assumption of 1% failure rate.</p>                                                                                                                                                                                                                                                       | <i>The lower limits for sLPC, cLPC and HPC were determined using S/N ratio PC/NC with 1% failure rate. This is acceptable.</i>                                                                                                            |
| HPC system suitability range                                                         | <p>S/N ratio <math>\geq 277.56</math></p> <p>%inhibition (%INH) <math>\geq CPP</math></p>                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                           |
| Screening cut-point (SCP): median NC response $\times$ normalization factor [1.6186] | <p>Fifty (50) individual human serum samples (25 male and 25 female) were evaluated by 2 analysts in each of 2 independent assay runs. The reported value for each test sample was the mean ECL response from duplicate wells on a plate. A total of 200 individual ECL values were generated.</p> <p>A robust parametric approach (lower confidence limit (LCL) formula) was used to determine SCP</p>                                                                              | <i>The approach for SCP normalization factor determination is acceptable as it included relevant sources of variation such as analyst, plate, and date of run. Use of 5% FPR for SCP normalization factor determination is acceptable</i> |

|                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|---------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                           | <p>normalization factor using 5% false positive rate (FPR). The normalization factor was calculated using the log-transformed S/N ratio values after outlier removal. The SCP factor was determined to be 1.6186.</p> <p>NC was used to adjust the SCP on each plate to determine the PSCP as follow:<br/> <math>PSCP = 1.6186 \times \text{median plate NC ECL}</math></p>                                                                                                                                                                                                           | <p><i>and consistent with the FDA 2019 immunogenicity assay guidance.</i></p> <p><i>Based on SCP normalization factor of 1.6186 for calculating PSCP, the initial clinical immunogenicity data show that the baseline ADA rate was 3.5% (3/86) when using the pre-study cut point, which is within 2-11% FPR. This shows the pre-study validation SCP normalization and the NC values were suitable for ADA screening test of clinical samples.</i></p> |
| Confirmatory cut-point (CCP)<br>Floating                                  | <p>Fifty (50) individual human serum samples (25 male and 25 female) un-spiked (same samples used for SCP) and spiked with excess JZP-458 (8.0µg/mL) were tested at least 1 replicate in at least 2 runs performed by 2 different analysts (total of at least 4 runs). The mean ECL with and without JZP-458 was compared, and the % INH (CCP) calculated for the individual serum samples. The NC was analyzed 3 times in duplicate (spiked and un-spiked) on all CCP plates.</p> <p>The CCP of 55.35% was determined statistically by LCL robust parametric approach at 1% FPR.</p> | <p><i>The CCP determination incorporated the relevant variability such as samples, analysts, runs, and plates, etc. and used 1% FPR, which is acceptable and consistent with the FDA 2019 assay guidance.</i></p>                                                                                                                                                                                                                                       |
| Titer cut point (TCP): median NC response × normalization factor [2.4323] | <p>TCP factor of 2.4323 was estimated using the same data and statistical methods (LCL robust parametric) used to establish the SCP normalization factor but with a more stringent FPR (0.1% FPR).</p> <p>NC was used to adjust the TCP on each plate to determine the PSTCP as follow:<br/> <math>PSTCP = 2.4323 \times \text{median plate NC ECL}</math></p>                                                                                                                                                                                                                        | <p><i>TCP normalization factor was determined data from SCP determination but with 0.1% FPR. This is acceptable.</i></p>                                                                                                                                                                                                                                                                                                                                |
| Sensitivity                                                               | <p>PC antibody was spiked into pooled human serum and twofold serially diluted using 100% human serum from 500.00 ng/mL to 0.015 ng/mL to span the screening cut point.</p>                                                                                                                                                                                                                                                                                                                                                                                                           | <p><i>The assay is highly sensitive to detect and confirm &lt; 1 ng/mL ADA (0.340 ng/mL at screening and 0.508 ng/mL at confirmatory testing).</i></p>                                                                                                                                                                                                                                                                                                  |

|                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
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|                      | <p>A total of 12 sensitivity runs were conducted by 2 analysts (3 preparations, at two occasions). Each dilution was assayed in duplicate in the absence and presence of excess JZP-458, according to the confirmatory assay procedure. The screening assay sensitivity was determined using a 5-parametric logistic (5-PL) regression of ECL signal vs. PC antibody body concentration.</p> <p>The screening assay sensitivity was calculated from all runs as follow:<br/> Mean PC concentration at PSCP + (t<sub>0.05</sub>, df X SD)</p> <p>Confirmatory assay sensitivity was calculated from all run as follow:<br/> Mean PC concentration at CCP + (t<sub>0.05</sub>, df X SD)</p> <p>Sensitivity of the screening assay and confirmatory assay was determined to be 0.340 ng/mL and 0.508 ng/mL, respectively.</p> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| Assay Drug tolerance | <p>Drug tolerance of the assay was determined by spiking the sLPC/cLPC and HPC with 800.00µg/mL to 0.02µg/mL JZP-458 (2-fold serial dilution). Each dilution was assayed in duplicate.</p> <p>At HPC (250 µg/mL), the screening drug tolerance was 100 µg/mL and the confirmatory drug tolerance was 25 µg/mL JZP-458.</p> <p>At sLPC (0.60 ng/mL), the screening drug tolerance was 0.20 µg/mL JZP-458.</p> <p>At cLPC (0.80 µg/mL), the confirmatory drug tolerance was &lt;0.02 µg/mL JZP-458.</p>                                                                                                                                                                                                                                                                                                                      | <p><i>The method validation results show that the presence of JZP-458 drug could suppress the signal of PCs. Screening assay tolerated drug concentration was shown as 0.2 µg/mL (200 ng/mL). The confirmatory assay was found to be affected with drug concentration &gt;0.02 µg/mL (20 ng/mL). The trough level of JZP-458 was expected to be ≤1 ng/mL before starting subsequent treatment course when ADA samples collected. However, OSIS Remote Record Report shows that ~40% of samples analyzed in the ADA confirmatory assay had drug levels within the range of 1-1802 ng/mL, suggesting that the levels of drug concentrations in study samples were above the assay drug tolerance established during method validation. This would potentially result in</i></p> |

|                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
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|                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | <i>underestimation of ADA. Drug tolerance issue will be addressed by PMC (See PMCs below)</i>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| Selectivity                           | <p>For matrix interference, sLPC and HPC concentration for screening assay, and cLPC and HPC for confirmatory assay were spiked into ten (10) lots of individual human serum (5 males and 5 females).</p> <p>For the evaluation of hemolysis, NC or a lot passing selectivity was spiked with 5% red blood cells (1100 mg Hb/dL) and 1 lot of lipemic human serum was spiked at the sLPC and HPC concentrations (for the screening assay) and cLPC and HPC concentrations (for the confirmatory assay).</p> <p>Screening assay acceptance criteria:<br/>Un-spiked samples – mean ECL &lt;PSCP for at least 90% of the individual lots and for each of the hemolyzed or lipemic lots</p> <p>Acceptance criteria for PC spiked samples: a precision of <math>\leq 20\%</math> CV between duplicate wells and mean response <math>\geq</math> PSCP for at least 80% of the individual lots analyzed at each level, and for each of the hemolyzed or lipemic lots at each concentration.</p> <p>Confirmatory assay AC:<br/>blank samples &gt; 90% with % Inhibition &lt; CCP and for each of the hemolyzed and lipemic lots.<br/>PC spiked samples % Inhibition &gt; CCP for &gt; 80% of individual lots and for each of the hemolyzed and lipemic lots</p> | <p><i>The un-spiked individuals did not meet the acceptance criteria for the screening assay (blank samples mean response &lt; PSCP for at least 90% of the individual lots), which indicates the FPR in screening may be &gt;5%. The confirmatory assay selectivity of un-spiked individuals was acceptable.</i></p> <p><i>Spiked selectivity (PC at 0.80 ng/mL) did not meet acceptance criteria for confirmatory assay (% Inhibition &gt; CCP for at least 80% of individual lots). At 2.00 ng/mL PC, selectivity acceptance criterion was met (100% of the individuals lots had % Inhibition &gt; CCP). This result show that the assay can still confirm very low levels of ADA (<math>\geq 2</math> ng/mL).</i></p> <p><i>Overall, the selectivity of the assay shows that there is matrix interference on ADA screening and confirmation, but the assay can still confirm as low as 2 ng/mL ADA. This is acceptable.</i></p> |
| Repeatability/Intra-assay variability | <p>Intra-assay precision (% CV) was evaluated using six duplicate sets (12 wells) at each PC concentration (sLPC, cLPC and HPC).</p> <p><u>Intra-assay acceptance criteria for the screening assay and results:</u></p> <p>ECL mean %CV <math>\leq 20\%</math>; Results: sLPC %CV=8.69%; HPC %CV= 17.4%</p> <p>ECL of 4 out 6 replicates <math>\geq</math> PSCP; Results: sLPC 6/6; HPC 6/6</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | <p><i>The intra-assay precision results all met the pre-defined acceptance criteria for screening assay and confirmatory assay at LPC and HPC levels.</i></p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |

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|                                                     | <p>ECL of sLPC &lt; ECL of HPC; Result:6/6</p> <p><u>Intra-assay acceptance criteria and results for the confirmatory assay:</u></p> <p>%CV of mean %INH <math>\leq</math>20%; Results: cLPC %CV= 10.81%; HPC %CV= 0.6%</p> <p>%INH of PCs 4 out 6 replicates <math>\geq</math>CPP Results: cLPC 5/6; HPC 6/6</p> <p>%INH of cLPC &lt;%INH of HPC; Result met acceptance criteria</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                   |
| Intermediate Precision (IP)/inter-assay variability | <p>Intermediate precision (inter-assay variability) for the control samples were evaluated using duplicates sets on 3 separate occasions by each of 2 analysts (a total of at least 6 occasions).</p> <p><u>Inter-assay acceptance criteria for the screening assay and results:</u></p> <p>Acceptance criteria mean ECL %CV<math>\leq</math>20%<br/>Results: sLPC %CV =6.19 %<br/>HPC %CV =15.08%<br/>cLPC %CV=7.42%<br/>NC %CV=8.74%</p> <p>Acceptance criteria S/N %CV<math>\leq</math>20%<br/>sLPC %CV =8.23 %<br/>HPC %CV =19.49%<br/>cLPC %CV=11.28%</p> <p>ECL of 3 out 4 on each plate <math>\geq</math>PSCP; result- met<br/>sLPC ECL &lt; ECL of HPC; result- met</p> <p><u>Inter-assay acceptance criteria for the confirmatory assay and results:</u></p> <p>%CV of cLPC <math>\leq</math>20%; result %CV=7.14%<br/>%CV of HPC&lt;20%; result %CV=1.64%<br/>%INH of PCs 3 out 4 on each plate <math>\geq</math>CPP; result- met<br/>%INH of cLPC &lt;%INH of HPC; result- met</p> | <p><i>All intermediate precision results met the pre-defined acceptance criteria of CV%<math>\leq</math>20% and acceptance criteria for mean ECL signal. The assay has acceptable intermediate precision.</i></p> |

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| Titer Determination and Precision | <p>Titer determination and precision were evaluated by titrating of the HPC in human serum. HPC was diluted serially, 10-fold, 1200-fold, 2400-fold, 4800-fold, 9600-fold, 19200-fold, 38400-fold, through 76800-fold using 8 separate runs performed by 2 analysts.</p> <p>Acceptance criterion: the titer of the PC had to remain within <math>\pm 1</math> dilution for all analyses.</p> <p>Using PSTCP, the HCP titer was determined to be 1865-fold (933-fold to 3731-fold).</p>                                                                                                                                                                                                                                                                                                                                                                                                                                            | <i>The titers were determined by twofold dilution and all titers determined for HPC were within <math>\pm 1</math> dilution, which indicates the titration precision is acceptable.</i> |
| Stability                         | <p>Sample stability during sample analysis was evaluated using sLPC in screening assay and HPC in the titer assay with 3 replicates (6 wells) per level.</p> <p><u>Freeze-thaw stability in human serum:</u><br/> 6 cycles stored at -60°C to -80°C, thawed at RT<br/> 6 cycles stored at -10°C to -30°C, thawed at RT</p> <p><u>Short-term stability in human serum:</u><br/> The short-term stability was evaluated for samples kept at RT for about 19 hours and 16 minutes</p> <p><u>Acceptance criteria:</u> %CV <math>\leq</math> 20% for replicates of PC samples and sLPC mean ECL <math>\geq</math> PSCP; HPC titer within determined titer of 933-fold to 3731-fold.</p> <p>The %CV (0.542% to 2.16%) and the mean ECL value met the acceptance criteria for sLPC. The titers for HPC duplicates were within the determined titer of 933-fold to 3731-fold.</p> <p>All results met pre-defined acceptance criteria.</p> | <i>The results show that the samples are stable during 6 cycles of freeze-thawing, and storage at RT for up to 19:26 hrs.</i>                                                           |
| Lipemia                           | <p>Impact of lipemia was evaluated under selectivity assessment. Lipemic human serum un-spiked with PC or spiked with PCs (of sLPC, cLPC and HPC) were assessed. All results met acceptance criteria:</p> <p>Un-spiked lipemic serum ECL &lt; PSCP;<br/> %INH &lt; 55.35%</p> <p>sLPC, cLPC and HPC spiked lipemic serum ECL &gt; PSCP; %CV <math>\leq</math> 20% and %INH &gt; 55.35%.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | <i>Data show that lipemia does not impact ADA detection.</i>                                                                                                                            |
| Hemolysis                         | <p>Impact of hemolysis was evaluated under selectivity assessment. sLPC, cLPC and HPC were spiked in</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | <i>Data show that hemolysis does not impact ADA detection.</i>                                                                                                                          |

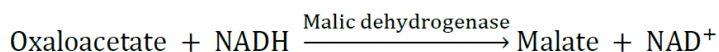
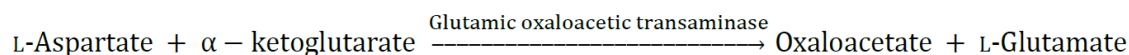
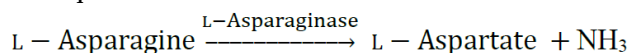
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|                           | <p>human serum, which was negative or passed selectivity, to which 5% red blood cells (1100 mg Hb/dL) was added.</p> <p>All results met acceptance criteria:<br/> Un-spiked hemolyzed serum ECL &lt; PSCP;<br/> %INH&lt;55.35%<br/> sLPC, cLPC and HPC spiked hemolyzed serum ECL≥PSCP; %CV≤20% and %INH&gt;55.35%.</p>                                                                                                                                                                                                                      |                                                                                                                                                                                                                |
| Ruggedness and Robustness | <p>Different incubation times (±10%) for the spiked master mix sample and samples to MSD plate steps were evaluated for assay robustness.</p> <p>Different MSD readers, plate washers, lots of MSD plates and different lots of reagents and two analysts were evaluated for assay ruggedness</p> <p>Controls on all plates met routine acceptance criteria.</p>                                                                                                                                                                             | <i>Data show that the assay is robust with various incubation times and it is impacted by the use of different MSD readers, plate washers, lots of MSD plates and different lots of reagents and analysts.</i> |
| ADA Assay Assessment      | <p><b>The method is validated for specificity, selectivity, cut-point and titer determination, precision, sensitivity, stability, and robustness. However, the method is not suitable for detection, confirmation, and titering of anti-JZP-458 antibodies in presence of expected JZP-458 levels in patient serum at the time of sampling. This is not approvability issue given the observed acceptable safety profile and lack of actionable information based on ADA status. This drug tolerance issue will be addressed by PMC.</b></p> |                                                                                                                                                                                                                |

## 2.3 Validation of Neutralizing Antibody Assay

A method for the detection of neutralizing anti-JZP-458 antibodies (NAb) in human serum was validated at (b) (4) who also conducted testing of the clinical samples. A signed validation report (Report Number: 00350549) dated September 30, 2020 for this NAb assay is submitted in section 5.3.1.4. A total of 18 analytical runs were performed and all met assay acceptance criteria.

### 2.3.1 Method Principle

The method utilized an enzymatic activity assay technique for detection of NAb to JZP-458 in human serum. L-asparaginase activity was quantified based on the rate of NADH conversion to NAD<sup>+</sup> from the following reaction:



Absorbance at 340 nm was measured and Vmax (rate in OD/min) was calculated. The method was adapted from a quantitative method validated for the determination of serum asparaginase assay (SAA) of JZP-458 for measuring NAb.

The rabbit polyclonal (monospecific, IgG) antibody used for the ADA assay was shown have weak neutralizing activity of the JZP-458 L-asparaginase activity. Samples are pre-treated (IgG is purified) using a 96-well Melon Gel spin plate to separate antibodies from drug. To conduct pretreatment, PCs and NC were diluted 6-fold and processed through a 96-well Melon Gel spin plate. The spin plate pretreated samples were mixed with a constant concentration of JZP-458 and enzymatic mixture (glutamic oxaloacetate transaminase and malic dehydrogenase with their substrates) to measure the neutralizing activity of the samples.

### 2.3.2 Validation Exercises

**Table 2.2: Validation Results and Reviewer Assessment for NAb Assays Used in Study JZP458-201**

| Validation Parameter  | Validation Report: 00350549                                                                                                                                                                                                                                                                                           | Reviewer Comment                                                                                                                                                                                                                                                                                   |
|-----------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Contract Research Org | (b) (4)                                                                                                                                                                                                                                                                                                               | <i>Clinical samples were analyzed at this site.</i>                                                                                                                                                                                                                                                |
| Assay principle       | Kinetic enzymatic assay: NAb inhibits the L-asparaginase enzymatic of JZP-458                                                                                                                                                                                                                                         | <i>The presumed mode of action for JZP-458 is through its L-asparaginase activity, so the selected NAb assay is appropriate.</i>                                                                                                                                                                   |
| Sample Pretreatment   | The samples were pretreated (Melon Gel Spin Plate Kit for IgG Screening, IgG purification) to overcome drug tolerance. The pretreatment of the samples improved drug tolerance by 10-fold at the LPC level and about 100-fold at the HPC level. Heat and acid treatment did not significantly improve drug tolerance. | <i>Pretreatment may result in loss ADA. In IR response SN0042 the Applicant stated that the use of the Melon Gel Spin purification increased sensitivity. However, the Applicant did not provide evidence for no ADA loss. The Applicant agreed to address this issue in PMC (See PMCs below).</i> |
| Positive control (PC) | Monospecific anti-Erwinaze Rabbit IgG<br>EUSAERWIGG1106001043012<br>Storage: -60°C to -80°C                                                                                                                                                                                                                           | <i>The same antibody lot was used for both ADA assay and NAb assay.</i>                                                                                                                                                                                                                            |
| Reference standard    | JZP-458 lot CMC-M0002<br>Storage: -10°C to -30°C<br>Retest date: 06/30/2021                                                                                                                                                                                                                                           | <i>The same JZP-458 lot was used for both ADA assay and NAb assay.</i>                                                                                                                                                                                                                             |

|                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                      |
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| Positive controls (LPC and HPC)                         | <p>LPC level was calculated using sensitivity results as follow:</p> <p>LPC level = Mean PC concentration at NCP + (t0.01,df × SD)</p> <p>LPC= 5,000 ng/mL</p> <p>HPC: 100,000 ng/mL</p>                                                                                                                                                                                                                                                                                                                                                           | <i>The LPC concentration of 5,000 ng/mL was determined using the assay sensitivity level with 1% assay rejection rate, which is acceptable as per 2019 FDA assay guidance and a common industry practice.</i>                                        |
| Matrix and NC                                           | Human serum                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | <i>The use of human serum as the matrix control is acceptable.</i>                                                                                                                                                                                   |
| MRD                                                     | 28.2-fold                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | <i>Acceptable.</i>                                                                                                                                                                                                                                   |
| NC system suitability range                             | At least 2/3 duplicates precision between wells ≤20% CV                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | <i>LPC was determined based on 1% failure rate. The system suitability acceptance criteria also include: <math>NC \leq NCP \leq LPC &lt; HPC</math>. This is acceptable.</i>                                                                         |
| Acceptance criteria for positive controls (LPC and HPC) | <p>Acceptance criteria for PCs (LPC and HPC) in the assay was determined using mean %INH and SDs of PCs from all validation runs (excepts runs used in sensitivity and cut points for human matrices).</p> <ul style="list-style-type: none"> <li>LPC was set at 1% failure rate and the acceptance criterion was set as <math>LPC \%INH \geq NCP</math></li> <li>HPC acceptance criterion was calculated to be <math>HPC \%INH \geq 27.53\%</math> using the following formula:</li> </ul> <p>Lower Limit = Mean % Inhibition - t0.01,df × SD</p> |                                                                                                                                                                                                                                                      |
| NAb assay cut- point (NCP)                              | NCP is the % INH at or above which a sample was defined to be NAb positive. NCP was determined using fifty (50) individual serum samples (25 female and 15 male) and a normal serum pool negative control (NC). Each sample was evaluated by 2 analysts over 3 separate experiments for Vmax. The NCP was determined statistically using a 1% false positive rate (FPR) with 80% confidence after outlier removal. The calculated mean NCP Vmax was 9.03.                                                                                          | <i>NCP was set based on 1% FPR, which is acceptable as 2019 FDA guidance and common industry practice.</i>                                                                                                                                           |
| Assay Drug tolerance                                    | Drug tolerance (the concentration of JZP-458 present without masking the ant-JZP-458 antibodies) was evaluated by spiking the LPC and HPC with JZP-458 and serially diluting (2-fold, to 8 dilutions) with un-spiked preparations of each PC (LPC and HPC), and incubated for 30 minutes. The JZP-458 concentration in the                                                                                                                                                                                                                         | <i>The trough level of JZP-458 was expected to be ≤1 ng/mL before starting subsequent treatment course when ADA samples collected. However, OSIS Remote Record Report shows that ~40% of samples analyzed in the ADA confirmatory assay had drug</i> |

|                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                             |
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|                                       | <p>PC that demonstrated a % INH <math>\geq</math> NCP was the JZP-458 concentration that can be tolerated by assay.</p> <p>Drug tolerance for the LPC and the HPC was determined to 156.25 ng/mL and 6250 ng/mL.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                          | <p><i>levels within the range of 1-1802 ng/mL. Since the samples tested in the NAb assay were a subset of samples tested in the ADA confirmatory assay, the NAb assay may also have the drug tolerance issue. This issue will be addressed by PMC (See PMCs below).</i></p> |
| Sensitivity                           | <p>Sensitivity (lowest concentration NAb that can be detected) was tested by analyzing PC curves by 3 preparations by two analysts on three occasions (12 sensitivity curves total). Anti-JZP-458 antibodies were spiked into pooled human serum and serially diluted 2-fold using 100% human serum: 40,000, 20,000, 10,000, 5,000, 2,500, 1,250, 625, 312.5ng/mL PC were prepared by spiking PC into pooled human serum</p> <p>Six (6) runs were performed by two analysts over three separate days.</p> <p>Sensitivity was calculated as 3,742 ng/mL using the formula below:</p> <p>Mean PC concentration at NCP+ (<math>t_{0.05,df} \times SD</math>)</p> | <p><i>Sensitivity was calculated using the 5% failure rate, which is consistent with current common practice and FDA guidance. It is acceptable.</i></p>                                                                                                                    |
| Repeatability/Intra-assay variability | <p>Intra-Assay precision was evaluated by running six duplicate sets (12 wells) at each PC concentrations (LPC and HPC) in a single validation run and measured as %CV.</p> <p><u>Acceptance criteria:</u> % CV of the mean Vmax of each PC level <math>\leq</math> 20%</p> <p>Results: LPC %CV of Vmax = 3.4%<br/>HPC %CV of Vmax= 2.05%</p> <p><u>Acceptance criteria:</u> %INH of PCs (for at least 4/6 duplicates) <math>\geq</math> NCP</p> <p>Result: acceptance criteria met</p> <p>Acceptance criteria: %INH of LPC &lt; %INH of HPC</p> <p>Result: acceptance criteria met</p>                                                                       | <p><i>All the results met the predefined acceptance criteria, and the assay was shown to have acceptable repeatability.</i></p>                                                                                                                                             |

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| Intermediate Precision (IP)/inter-assay variability | <p>The inter-assay precision was evaluated by running two duplicate sets at each PC concentration on three separate occasions by two analysts.</p> <p>% CV of the mean Vmax of each PC level <math>\leq 20\%</math></p> <p>%INH of PCs (3/4 on each plate) <math>\geq</math> NCP</p> <p>%INH of LPC <math>&lt;</math> %INH of HPC</p> <p>The overall inter-assay was calculated for NC.</p> <p>Not all results met acceptance criteria. The %CV of the mean Vmax results for LPC and HPC were <math>\geq 20\%</math>CV and <math>\leq 25\%</math>CV.</p>                                                                                            | <p><i>Not all the results for inter-assay precision met the criteria for %CV of Vmax <math>\leq 20</math>. The cause for higher variability was spin plate incubation for 4 minutes for one plate, which failed the acceptance criteria. The spin plate incubation time was limited to 5-6 minutes to mitigate the impact of shorten incubation on assay variability. Excluding the plate with shortened incubation, all the results met the assay acceptance criteria.</i></p> |
| Selectivity                                         | <p>Ten (10) individual human serum samples (5 female and 5 male) were spiked with LPC/HPC; NC was spiked with 5% whole blood and 1 lot lipemic human serum at LPC and HPC. All samples and blank serum were assayed in duplicate in a single run.</p> <p>All PC spiked, hemolyzed, and lipemic samples met acceptance criteria: blank %INH <math>&lt;</math> NCP for at least 90% and for each of the hemolyzed or lipemic lots; LPC and HPC %INH <math>\geq</math> NCP at least for 80% of the individual lots analyzed at each level PC, and for each of the hemolyzed or lipemic lots at each concentration; all %CV <math>\leq 20\%</math>.</p> | <p><i>All acceptance criteria were met, so matrix interference was not detected including for hemolyzed and lipemic sera.</i></p>                                                                                                                                                                                                                                                                                                                                               |
| Stability                                           | Not required in this study. Stability was evaluated in ADA assay for JZP-458.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Acceptable                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Ruggedness and Robustness                           | <p>The ruggedness of the NAb assay was evaluated by utilizing two analysts, 2 different plate readers and 2 different lots of enzyme mix. The robustness of the assay was assessed by varying the incubation times.</p> <p>The results of all runs met the acceptance criteria except for inter-assay precision of the Vmax, which did not meet acceptance criteria for all runs, but met the acceptance criteria when the plate evaluated for short incubation time (4 min) for the spin plate was excluded. The assay was found to not robust for shorter</p>                                                                                     | <p><i>The assay was found to be robust for the parameters range assessed except for shorter (4 min) incubation time for the spin plate (sample pretreatment step) as the result the incubation time for this step was limited to 5-6 min, which is acceptable.</i></p>                                                                                                                                                                                                          |

|                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |  |
|----------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|
|                      | incubation time, and the incubation time was limited to 5-6 min.                                                                                                                                                                                                                                                                                                                                                                                                                                             |  |
| NAb Assay Assessment | <b>The NAb assay is validated for cut-point determination, precision, sensitivity, selectivity, stability, and robustness. However, the method may not be suitable for detection of neutralizing antibodies against JZP-458 in presence of expected JZP-458 levels in patient serum at the time of sampling. This is not an approvability issue given the observed acceptable safety profile and lack of actionable information based on ADA status. This drug tolerance issue will be addressed by PMC.</b> |  |

## 2.4 Facility Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) conducted a remote record review (RRR) of ADA/Nab assays as well as serum asparaginase activity (SAA) assay, and serum asparaginase content (SAC) assays assessing the samples from studies JZP458-101 and JZP458-201 conducted at (b) (4).

OSIS identified two objectionable conditions that impact the reliability of some study data.

1. The drug tolerance established in method validation for ADA was not adequate to cover drug concentrations observed in the patient samples. In study JZP458-201, 35% (108 of 305 samples) of samples analyzed in the ADA screening assay had drug concentrations above the drug tolerance (200 ng/mL) established at the LPC level. In addition, 40% (27 of 67 samples) of samples analyzed in the ADA confirmatory assay had drug concentrations within the range of 1.0 - 1802 ng/mL, among which 21 samples had drug concentrations above confirmatory drug tolerance (<20 ng/mL). (b) (4) acknowledged the observation and agreed to further evaluate the drug tolerance. The NAb assay also appears to have a drug tolerance issue: all samples with drug concentrations above drug tolerance established in method validation were negative for NAb (See PMC below).
2. The firm did not evaluate potential interference of ADA on measurement of JZP-458. The samples with ADA confirmed positive had low levels JZP-458 in the serum.

## 2.5 Assessment of Assay performance in Clinical Studies

### 2.5.1 Executive Summary

Assessor comments:

- The preliminary immunogenicity assessment shows that there was a high ADA rate toward JZP-458 (27/86, 31%). Two of the 27 JZP-458 treatment patients positive for ADA had reduced SAA without having NAb activity. Three of the 27 ADA positive patients had NAb but the SAA level in these patients was not impacted.
- The following issues were identified during assessment of method validation reports (OBP) and by FDA/OTS/OSIS colleagues when they performed remote record review of these assays and PK/PD assays:
  - o The ADA/NAb assays had inadequate drug tolerance.

- *The ADA and the JZP-458 are interfering with detection of each other: JZP-458 interferes with the measurement of ADA, and the ADA interferes with the measurement of JZP-458, which impact the interpretation of the clinical immunogenicity data.*
  - *The Melon Spin method used for mitigation of drug tolerance in NAb analysis was not evaluated for its impact on recovery of ADA against JZP-458.*
- *These findings are not approvability issues given the observed acceptable safety profile and lack of actionable information based on ADA status. To address these issues, the following PMCs are under discussion with the Applicant as of the time of finalizing this memo:*

**PMC#1 Rationale:** The immunogenicity assay used to screen, confirm and titer the binding ADA had insufficient drug tolerance for the observed JZP-458 concentration at the time of ADA sampling in Study JZP458-201. Specifically, for samples with time-matched ADA and PK samples, 119 out of 416 (28.6%) screening ADA samples and 22 out of 101 (21.8%) confirmatory ADA samples had JZP-458 concentration above the validated drug tolerance. Samples testing negative in the binding ADA assay with drug concentration above the drug tolerance may be false negatives.

**PMC#1:** Develop and validate a binding anti-drug antibody (ADA) assay with sufficient drug tolerance to be able to detect, confirm, and titer anti-RYLAZE binding antibodies in the presence of RYLAZE concentrations in clinical samples at the time of sampling.

**PMC#2 Rationale:** The immunogenicity assay used to determine presence of neutralizing antibodies (NAb) against JZP-458 had insufficient drug tolerance for the observed JZP-458 concentration at the time of ADA sampling in Study JZP458-201. Specifically, for samples with time-matched ADA and PK samples, 10 out of 70 (14.3%) NAb samples had JZP-458 concentration above the validated drug tolerance. Samples testing negative in the NAb assay with drug concentration above the drug tolerance may be false negatives.

**PMC#2:** Develop and validate a neutralizing ADA (NAb) assay with sufficient drug tolerance to detect neutralizing antibodies against RYLAZE in the presence of expected RYLAZE concentrations in clinical samples at the time of sampling.

**PMC#3 Rationale:** The Melon Gel Spin Plate Kit is used to pretreat serum sample to dissociate ADA from on-board JZP-458. This pretreatment approach has been shown to increase sensitivity of the neutralizing ADA (NAb) assay. However, Jazz did not provide direct evidence for no ADA loss by this pretreatment approach. The incidence of NAb may be underestimated if ADA cannot be sufficiently recovered from the Melon Gel Spin Plate Kit. Data for recovery of anti-JZP458 antibodies from serum samples pretreated with Melon Gel Spin Plate Kit are needed to determine the adequacy of NAb rate for the clinical studies.

**PMC#3:** Conduct a study examining quantitative recovery of anti-JZP458 antibodies from serum samples pretreated with Melon Gel Spin Plate Kit if immunogenicity data from an assay that uses the Melon Gel Spin Plate kit are used to support the license.

- *Because of the ADA/NAb assay drug tolerance issues and the ADA interference with SAC/SAA measurement, the SAC/SAA levels may be underestimated, which is unlikely to negatively impact, as this is a worst-case scenario for PK/PD.*

## 2.6 Information Requests Sent During Review



Zhenzhen  
Liu

Digitally signed by Zhenzhen Liu

Date: 6/29/2021 10:12:16AM

GUID: 555108d8007bb3724ef2a6d3413e2758



Susan  
Kirshner

Digitally signed by Susan Kirshner

Date: 6/29/2021 10:41:41AM

GUID: 508da6db000266b77da0ba4bfa620030

**BLA STN 761179**

**RYLAZE**

**(asparaginase erwinia chrysanthemi (recombinant)-rywn**

**Jazz Pharmaceuticals Ireland Limited**

**Mekonnen Lemma Dechassa, Ph.D., Biologist**

**Zhenzhen Liu, Ph.D., Team Lead**

**Division of Biotechnology Research and Review III**

## OBP Product Quality Assessment Data Sheet

1. **BLA#:** SN 761179
2. **ASSESSMENT DATE:** June 23, 2021
3. **PRIMARY ASSESSMENT TEAM:**

### Quality Assessment Team

| Discipline                  | Assessor                                                                                                   | Branch/Division                                                     |
|-----------------------------|------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------|
| Product Quality (DS and DP) | Mekonnen Lemma Dechassa                                                                                    | CDER/OPQ/OBP/DBRR III                                               |
| Immunogenicity              | Mekonnen Lemma Dechassa                                                                                    | CDER/OPQ/OBP/DBRR III                                               |
| Labeling                    | CAPT Vicky Borders Hemphill                                                                                | CDER/OPQ/OBP                                                        |
| Facility                    | Michael Shanks                                                                                             | CDER/OPQ/OPMA/DBM                                                   |
| Microbiology                | Reyes Candau-Chacon                                                                                        | CDER/OPQ/OPMA/DBM                                                   |
| Team Lead                   | Zhenzhen Liu (Product quality)<br>Zhenzhen Liu (Immunogenicity)<br>Virginia Carroll (Micro and Facilities) | CDER/OPQ/OBP/DBRR III<br>CDER/OPQ/OBP/DBRR III<br>CDER/OPQ/OPMA/DBM |
| Application Technical Lead  | Zhenzhen Liu                                                                                               | CDER/OPQ/OBP/DBRR III                                               |
| OPQ RBPM                    | Teshara Bouie                                                                                              | CDER/OPQ/OPRO/DRBPMI/RBPMB2                                         |

### Multidisciplinary Assessment Team

| Discipline                   | Assessor                                                                                                        | Office/Division                                                |
|------------------------------|-----------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------|
| RPM                          | Esther Park                                                                                                     | CDER/OND/ORO/ROOD                                              |
| Cross-disciplinary Team Lead | Donna Przepiorka                                                                                                | CDER/OND/ODD/DHM1                                              |
| Medical Officer              | Cara Rabik                                                                                                      | CDER/OND/ODD/DHM1                                              |
| Pharmacology/Toxicology      | Michael Manning / Brenda Gehrke                                                                                 | CDER/OND/ODD/DHOT                                              |
| Clinical Pharmacology        | Lauren Price / Xiling Jiang, Lanre Okusanya (TL)<br>Liang Li / Lian Ma (TL)<br>Melkamu Getie Kehtie, Stanley Au | CDER/OTS/OCPI/DCPI<br>CDER/OTS/OCPI/DPM<br>CDER/OTS/OSIS/DGDSI |
| Statistics                   | Haiyan Chen / Jonathon Vallejo, Lisa Rodriguez                                                                  | CDER/OTS/OB/DBIX                                               |

#### 4. MAJOR GRMP DEADLINES:

- |                          |                |
|--------------------------|----------------|
| a. Filing Meeting:       | May 10, 2021   |
| b. Mid-cycle meeting:    | May 21, 2021   |
| c. Wrap-up meeting:      | June 18, 2021  |
| d. Primary review due:   | June 16, 2021  |
| e. Secondary review due: | June 18, 2021  |
| f. PDUFA action date:    | April 30, 2022 |

#### 5. COMMUNICATIONS WITH APPLICANT AND OND:

| Communication/Document:               | Date:      |
|---------------------------------------|------------|
| Filing Letter                         | 05/18/2021 |
| Post mid-cycle communication          | N/A        |
| Applicant Teleconference              | 06/10/2021 |
| Product Quality Information Request 1 | 03/12/2021 |

|                                       |            |
|---------------------------------------|------------|
| Product Quality Information Request 2 | 04/28/2021 |
| Product Quality Information Request 3 | 06/01/2021 |
| Product Quality Information Request 4 | 06/04/2021 |
| Product Quality Information Request 5 | 06/08/2021 |
| Product Quality Information Request 6 | 06/15/2021 |
| Product Quality Information Request 7 | 06/16/2021 |
| Product Quality Information Request 8 | 06/16/2021 |

## 6. SUBMISSION ASSESSED:

| Submission:                      | Date Received: | Assessment Completed<br>(yes or no) |
|----------------------------------|----------------|-------------------------------------|
| Module 3 RTOR Submission         |                |                                     |
| Original BLA STN 761179/0003     | 12/18/2020     | yes                                 |
| Response to IR 1 STN 761179/0019 | 03/23/2020     | yes                                 |
| Response to IR 2 STN 761179/0028 | 05/07/2021     | yes                                 |
| Response to IR 3 STN 761179/0040 | 06/07/2021     | yes                                 |
| Response to IR 4 STN 761179/0042 | 06/08/2021     | yes                                 |
| Response to IR 5 STN 761179/0045 | 06/15/2021     | yes                                 |
| Response to IR 6 STN 761179/0048 | 06/16/2021     | yes                                 |
| Response to IR 7 STN 761179/0050 | 06/21/2021     | yes                                 |
| Response to IR 8 STN 761179/0051 | 06/21/2021     | yes                                 |

## 7. DRUG PRODUCT NAME/CODE/TYPE:

- a. Proprietary Name: RYLAZE
- b. Trade Name: RYLAZE
- c. Non-Proprietary Name/USAN: asparaginase erwinia chrysanthemi (recombinant)-rywn
- d. CAS Name: Not provided
- e. Common Name: JZP-458
- f. INN Name: Not provided
- g. Compndial Name: Not applicable
- h. OBP systematic name: PROT P06608 (ASPG\_DICCH) L-ASPARAGINASE [JZP-458]
- i. Other names: RC-P, PF743, 5-0113

## 8. PHARMACOLOGICAL CATEGORY:

Enzyme Replacement Therapy  
(Asparaginase)

## 9. DOSAGE FORM:

Injection, liquid

## 10. STRENGTH/POTENCY:

- (i): The concentration/strength of the Drug Product: 20 mg/0.5mL in a single-use vial.
- (ii): Type of potency assay: The biological activity (L-asparaginase enzyme activity) is tested by Nessler assay, which measures the amount of L-asparagine hydrolyzed by asparaginase erwinia chrysanthemi (recombinant)-rywn to aspartic acid and ammonia

**11. ROUTE OF ADMINISTRATION:**

Intramuscular

**12. REFERENCED DRUG MASTER FILES (DMF):**

| DMF#    | DMF Holder | Item Referenced | Letter of Cross-Reference | Comments (status)                                                     |
|---------|------------|-----------------|---------------------------|-----------------------------------------------------------------------|
| (b) (4) |            |                 | Yes                       | Defers to OPMA                                                        |
|         |            |                 | Yes                       | Information in the BLA was adequate; no separate review was required. |
|         |            |                 | Yes                       | Information in the BLA was adequate; no separate review was required. |
|         |            |                 | Yes                       | Information in the BLA was adequate; no separate review was required. |

**13. INSPECTIONAL ACTIVITIES:**

A pre-license inspection (PLI) was conducted between (b) (4) the drug substance manufacturing facility for asparaginase erwinia chrysanthemi (recombinant)-rywn. The inspection was conducted by Michael Shanks (OPQ/OMPA) and Zhenzhen Liu (OPQ/OBP) and covered the manufacturing operations and testing of asparaginase erwinia chrysanthemi (recombinant)-rywn including the following five quality systems: Quality Procedures, Facilities and Equipment, Materials Management, Production Processes and Contamination Prevention, and Laboratory Controls. A 2-item FDA-483 was issued (See Appendix 1 for a copy of FDA-483). Both the initial and final classification of the inspection is “Approval”.

The Agency waived the PLI of (b) (4) the DP manufacturing facility for asparaginase erwinia chrysanthemi (recombinant)-rywn based on the facility’s compliance history, currently acceptable GMP status, and the aseptic manufacturing of other US-licensed product on the same fill and finish line (See Inspection waiver memo by Michael Shanks, OPQ/OPMA).

**14. CONSULTS REQUESTED BY OBP:** None

**15. QUALITY BY DESIGN ELEMENTS:**

The following was submitted in the identification of QbD elements (check any that apply):

|   |                                          |
|---|------------------------------------------|
|   | Design Space                             |
| x | Design of Experiments                    |
| x | Formal Risk Assessment/Risk Management   |
|   | Multivariate Statistical Process Control |
|   | Process Analytical Technology            |
|   | Expanded Change Protocol                 |

**16. PRECEDENTS:**

**17. ADMINISTRATIVE:**

| Name and Title                                                                                       | Signature and Date |
|------------------------------------------------------------------------------------------------------|--------------------|
| Zhenzhen Liu, PhD Team Leader<br>Office of Biotechnology Products<br>Division III                    |                    |
| Mekonnen Lemma Dechassa, PhD Primary<br>Reviewer<br>Office of Biotechnology Products<br>Division III |                    |

**Summary of Quality Assessments**

**I. Primary Assessor Summary Recommendation**

The Office of Biotechnology Products recommends approval of BLA 761179 for Rylaze (asparaginase erwinia chrysanthemi (recombinant)-rywn) manufactured by Jazz Pharmaceuticals Ireland Limited. The data submitted in this application are adequate to support the conclusion that the manufacture of Rylaze (asparaginase erwinia chrysanthemi (recombinant)-rywn) drug substance and drug product is well controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under conditions specified in the package insert.

The Office of Biotechnology Products recommends approval of the proposed lot release/stability specifications and stability protocols for asparaginase erwinia chrysanthemi (recombinant) drug substance and drug product. The Office of Biotechnology Products recommends an expiry period of 24 months at long-term condition (5°C).

**II. List of Deficiencies to be Communicated: None**

**III. List of Post-Marketing Commitments/Requirements:**

The applicant validated the RP-UHPLC method using DS samples with 50-150% of the nominal assay concentration. This approach assessed the linearity and range of absolute peak areas for purity and impurities. However, the relative % peak areas for purity and impurities do not change among samples

with different protein concentrations. As relative % peak areas of pre-peak and post-peak species in JZP-458 DS and DP may increase during storage, studies using either relevant pre-peak and post-peak species spiking samples or forced degradation samples should be conducted to guarantee appropriate method performance (e.g. precision and accuracy) not only at release but also during stability. To address this issue, the Applicant agreed to the following post-marketing commitment:

**PMC1:** To update the RP-UHPLC method validation to include impurities spiking study (e.g. pre-peaks and post-peaks are enriched to assess assay performance at different purity/impurity ratios). Final report submission: 06/30/2022.

#### **IV. Assessment of Common Technical Document- Quality Module 1**

##### **A. Environmental Assessment of Claim of Categorical Exclusion**

Jazz requested a categorical exclusion from the requirement of an Environmental Assessment under 21 CFR 25.31 (b), on the basis that the estimated concentrations of the substance at the point of entry into the aquatic environment will be below 1 part per billion (ppb). In addition, to the Applicant's knowledge, no extraordinary circumstances exist that may cause this action to have a significant effect on the quality of human environment. The claim of categorical exclusion is accepted.

#### **V. Primary Container Labeling Assessment**

The primary and secondary container labeling assessments were performed by Vicky Borders-Hemphill, OBP (See a separate Labeling assessment memo).

#### **VI. Assessment of Common Technical Document- Quality Module 3.2:**

This document contains the review of the information provided on asparaginase erwinia chrysanthemi (recombinant) drug substance (Section 3.2.S) and drug product (Section 3.2.P).

#### **VII. Assessment of Immunogenicity Assays- Module 5.3.1.4**

The immunogenicity assays assessment is documented in a separate assessment memo.

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## Description of Drug Substance and Drug Product

### S. Drug Substance

#### 3.2.S.1 General information

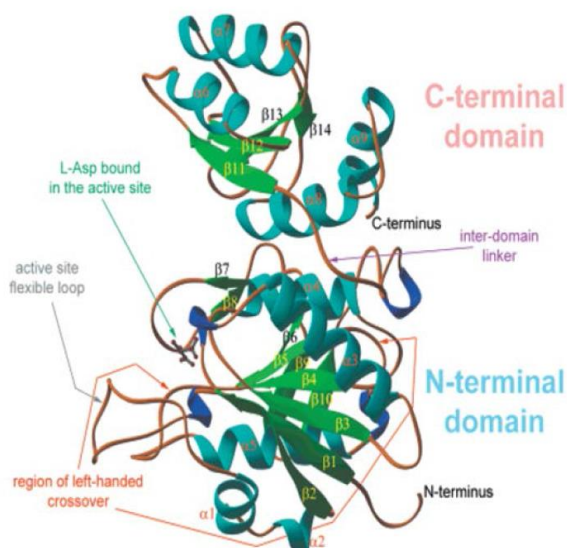
##### 3.2.S.1.2 Structure

Asparaginase erwinia chrysanthemi (recombinant) (here after JZP-458) is a tetrameric 140 kDa enzyme consisting of 4 subunits formed by noncovalent/non-disulfide interactions; the monomer has a molecular weight of 35 kDa. The amino acid sequence and schematic representation of the structure (monomer) are provided in Figures 1 and 2.

**Figure 1: Amino Acid Sequence**

|     | 10         | 20         | 30         | 40         |                |
|-----|------------|------------|------------|------------|----------------|
| 22  |            |            | ADKLPNIVI  | LATGGTIAGS | AATGTQTTGY 50  |
| 51  | KAGALGVDTL | INAVPEVKKL | ANVKGEQFSN | MASENMTGDV | VLKLSQRVNE 100 |
| 101 | LLARDDVDGV | VITHGTDTV  | ESAYFLHLTV | KSDKPVVFVA | AMRPATAISA 150 |
| 151 | DGPMNLLEAV | RVAGDKQSRG | RGVMVVLNDR | IGSARYITKT | NASTLDTFKA 200 |
| 201 | NEEGYLGVII | GNRIYYQNRI | DKLHTTTSVF | DVRGLTSLPK | VDILYGYQDD 250 |
| 251 | PEYLYDAAIQ | HGVKGIVYAG | MGAGSVSVRG | IAGMRKAMEK | GVVVIRSTRT 300 |
| 301 | GNGIVPPDEE | LPGLVSDSLN | PAHARILLML | ALTRTSDPKV | IQEYFHTY 348   |

**Figure 2: Schematic Representation of Crisantaspase Monomer**



### 3.2.S.1.3 General Properties

JZP-458 is a recombinant L-Asparaginase expressed in *Pseudomonas fluorescens*. The natural (non-recombinant) L-Asparaginase derived from *DicHEYA dadantii* (previously known as *Erwinia chrysanthemi*) is approved in Europe as crisantaspase/Erwinase and was licensed in the US as Erwinaze/Erwinia chrysanthemi L-Asparaginase.

The nomenclature of JZP-458 is provided in [Table 1](#). The properties of JZP-458 are provided in [Table 1](#). JZP-458 is a L-asparaginase that catalyzes L-asparagine to L-aspartic acid and ammonia. The biological activity is tested by Nessler assay, which measures the amount of L-asparagine hydrolyzed by JZP-458 to aspartic acid and ammonia.

L-Asparaginase is a vital component of multi-agent chemotherapy of childhood acute lymphoblastic leukemia/ Lymphoblastic Lymphoma (LBL). The native *E.coli* L-Asparaginase (Elspar) and pegaspargase (Oncaspar)- a pegylated form of *E.coli* L-asparaginase are used as the first line treatments. Erwinaze, naturally derived from the bacterium *DicHEYA dadantii* and has been used to treat patients with ALL who developed hypersensitivity to *E.coli* L-Asparaginase. JZP-458 is L-Asparaginase from *Erwinia chrysanthemi*, which is produced recombinantly in *Pseudomonas fluorescens*. The primary structure (amino acid sequence) of JZP-458 and Erwinaze is identical.

Leukemia cells are unable to make asparagine due to lack of asparagine synthetase activity. They are dependent on exogenous amino acid asparagine for their metabolism and survival. The mechanism of action of JZP-458 is thought to be by depleting asparagine in the circulation and depriving leukemia cells of asparagine amino acid. The normal cells can synthesize asparagine and are not affected by depletion of asparagine in the circulation.

## 3.2.S.2 Manufacture

### 3.2.S.2.1 Manufacturer(s)

Table 1: JZP-458 DS Manufacturers

| Manufacturer                         | Manufacturing site address                                           | Establishment Registration IDs               | Responsibility                                                                                                        |
|--------------------------------------|----------------------------------------------------------------------|----------------------------------------------|-----------------------------------------------------------------------------------------------------------------------|
| (b) (4)                              |                                                                      |                                              | Production of Drug Substance<br>Analytical, Release and Stability testing<br>Storage of Master and Working Cell Banks |
|                                      |                                                                      |                                              | Production and Initial Storage of the Master and Working Cell Banks                                                   |
|                                      |                                                                      |                                              | Enzyme Kinetics Assay ( $K_M/k_{cat}$ )                                                                               |
|                                      |                                                                      |                                              | Storage of Master and Working Cell Banks                                                                              |
| Jazz Pharmaceuticals Ireland Limited | Fifth Floor, Waterloo Exchange<br>Waterloo Road, Dublin 4<br>Ireland | FEI:<br>3012774443<br><br>DUNS:<br>896650210 | Release of commercial drug substance                                                                                  |

### 3.2.S.2.2, 3.2.S.2.4, 3.2.S.2.5, 3.2.S.2.6 Description of Manufacturing Process and Process Controls, Control of Critical Steps, Process Validation, Manufacturing Process Development

(b) (4)

## 3.2.P.8 Stability

### 3.2.P.8.1 Stability Summary and Conclusion

JZP-458 DP is stored at long-term storage condition of 2-8°C. The Applicant provided the DP stability data for long-term stability at 2-8°C for up to 36 months, accelerated stability at 25°C ± 5°C/60% RH ± 5% RH for 6 Months, stressed stability at 40°C ± 2°C/75% RH ± 5% RH for 2 months, photostability and in-use stability study (Section 3.2.P.2.6). The Applicant provided stability data for batches shown in [Table 1](#). GMP2 batch (AL4753) exhibited atypical stability profile and was not considered representative of future batches (See Section 3.2.S.2.6).

The Applicant proposed 24 months shelf life for JZP-458 DP at 2-8°C based on 30 months long-term stability data from AK0926 (GMP1) and 18C6003 (Engineering), and additional available 3-6 months long-term stability data from PPQ batches, and 6-12 from GMP3 and GMP4. (b) (4)

The stability protocol for JZP-458 DP is presented in Table 2 below.

**Table 2: Stability Protocol for JZP-458 Drug Product Engineering, GMP1, GMP2 and GMP3 Batches**

| Tests                                                                                                                                              | Initial | Stressed Condition<br>40°C ± 2°C/75%<br>RH ± 5% RH |    |    | Accelerated Condition<br>25°C ± 2°C/60% RH ±<br>5% RH |    |    |    | Long-term Condition<br>2-8°C |    |    |    |     |     |     |     |     |
|----------------------------------------------------------------------------------------------------------------------------------------------------|---------|----------------------------------------------------|----|----|-------------------------------------------------------|----|----|----|------------------------------|----|----|----|-----|-----|-----|-----|-----|
|                                                                                                                                                    |         | 2w                                                 | 1m | 2m | 1m                                                    | 2m | 3m | 6m | 1m                           | 3m | 6m | 9m | 12m | 18m | 24m | 30m | 36m |
| Appearance, pH, Osmolality, Specific Activity, Protein Concentration, RP-UHPLC, SE-UHPLC, CIEX-UHPLC, CE-SDS (reduced), Sub-visible Particle Count | ✓       | ✓                                                  | ✓  | ✓  | ✓                                                     | ✓  | ✓  | ✓  | ✓                            | ✓  | ✓  | ✓  | ✓   | ✓   | ✓   | ✓   | ✓   |
| Polysorbate 80 <sup>a</sup><br>K <sub>m</sub> /k <sub>cat</sub> <sup>a</sup>                                                                       | ✓       | ✓                                                  | ✓  | ✓  | ✓                                                     | ✓  | ✓  | ✓  | ✓                            | ✓  | ✓  | ✓  | ✓   | ✓   | ✓   | ✓   | ✓   |
| Bacterial Endotoxin, Sterility, Container Closure Integrity <sup>b</sup>                                                                           | ✓       |                                                    |    |    |                                                       |    |    |    |                              |    |    |    | ✓   |     | ✓   |     | ✓   |
| Extractable Volume                                                                                                                                 | ✓       |                                                    |    |    |                                                       |    |    |    |                              |    |    |    |     |     |     |     | ✓   |
| Gray shading: Tests not conducted                                                                                                                  |         |                                                    |    |    |                                                       |    |    |    |                              |    |    |    |     |     |     |     |     |

<sup>a</sup> Polysorbate 80 and K<sub>M</sub>/k<sub>cat</sub> tests conducted on GMP2 and GMP3 only. K<sub>M</sub>/k<sub>cat</sub> not tested at 2w due to timing constraints.

<sup>b</sup> Container-Closure Integrity test performed on Eng and GMP1 at all long-term time points. GMP2 and GMP3 will be tested according to the timepoints checked in the table.

**Photostability:** A photostability study was conducted by exposing DP to 1.2 million lux hours of light, at 2-8°C storage condition using test conditions shown in Table 3.

**Table 3: Testing Scheme for Photostability Study**

| Tests                                                                                                                                                               | Test Condition |              |        |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------|--------------|--------|
|                                                                                                                                                                     | Uncovered      | Dark Control | Carton |
| Appearance, pH, Osmolality, Specific Activity, Protein Conc. (OD279), RP-UHPLC, SE-UHPLC, CIEX-UHPLC, CE-SDS, Sub-visible particles, $K_M/k_{cat}$ , Polysorbate 80 | ✓              | ✓            | ✓      |

Statistical analysis of stability data for batches AM0383, AK0926 and 18C6003 was conducted to support the proposed shelf life of 24 months. Stability data and trends show that no substantial changes were observed after storage for up to 30 months at the recommended storage condition of 2-8°C. DP quality didn't change significantly up on exposure to light when stored in cartons. Changes were observed (within the specification) when uncovered vials were exposed to light.

*Assessor comment: The provided data which include 30 months stability from batches 2 (AK0926-GMP1 batch and 18C6003- engineering batch) and supporting additional available 3-6 months long-term stability data from PPQ batches, and 6-12 from GMP3 and GMP4 batches support the proposed 24 months shelf life at 2-8°C. All results at met specification at 2-8°C and no trends were observed. When stored in cartons representative of commercial packaging, JZP-458 is photostable.*

### 3.2.P.8.2 Post-Approval Stability Commitment

The Applicant committed to continue on going stability study as per described in 3.2.P.8.1 and to place at least one DP batch on stability every year and will be tested as protocol presented in Table 1 below.

**Table 1: Stability Protocol for Annual Stability Batches**

| Test                                                                                                                                                                             | Timepoints: M = Months               |                            |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------|----------------------------|
|                                                                                                                                                                                  | 2-8 °C Inverted                      | 25°C ± 2°C, 60% RH ± 5% RH |
| Appearance, pH, Osmolality, Specific Activity, Protein Concentration, RP-UHPLC, SE-UHPLC, CIEX-UHPLC, CE-SDS (reduced), Polysorbate 80, Sub-Visible Particles, and $K_M/k_{cat}$ | 0, 3, 6, 9, 12, 18, 24, 36, and 48 M | 0, 3 and 6 M               |
| Container Closure Integrity, Extractable Volume                                                                                                                                  | 0, 12, 24, 36 and 48 M               | Not tested                 |

The Applicant stated that prior to starting annual stability program, PPQ batches and the initial commercial batches will be assessed for stability using the protocol shown in Table 2.

**Table 2: Stability Protocol for PPQ and Initial Commercial batches**

| Tests <sup>a</sup>                                                                                                                                                                  | Timepoints: M = Months, W = Weeks       |                                  |                                  |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------|----------------------------------|----------------------------------|
|                                                                                                                                                                                     | 2-8°C<br>Inverted <sup>b</sup>          | 25°C ± 2°C,<br>60% RH ±<br>5% RH | 40°C ± 2°C,<br>75% RH ±<br>5% RH |
| Appearance, pH, Osmolality, Specific Activity, Protein concentration, RP-UHPLC, SE-UHPLC, CE-SDS (reduced), Polysorbate 80, Sub-Visible Particles, K <sub>M</sub> /k <sub>cat</sub> | 0, 1, 3, 6, 9, 12, 18, 24, 30, and 36 M | 0, 1, 2, 3, and 6 M              | 0, 2W <sup>c</sup> , 1M, 2M      |
| Container-Closure Integrity, Extractable Volume                                                                                                                                     | 0, 12, 24, and 36M                      | Not tested                       | Not tested                       |

<sup>a</sup> Release testing includes all listed tests.

<sup>b</sup> Commercial batches will be tested to 48M.

<sup>c</sup> Due to timing constraints, K<sub>M</sub>/k<sub>cat</sub> is not tested at 2 weeks.

The Applicant commits to report to the FDA any failure of a distributed drug product batch that fails to comply with established stability specifications.

*Assessor comments: The annual stability protocol is deficient because the proposed timepoints lacks recommended timepoints and no accelerated and stressed stability studies are proposed in order to detect unexpected instability that cannot be captured early under long-term condition. In the IR response SN0028 dated May 07, 2021, the Applicant updated the annual stability protocol by including the missing time points (consistent with ICH Q5C) and adding accelerated and stressed stability studies.*

### 3.2.P.8.3 Stability Data:

The Applicant provided tabulated stability data for DP batches shown in Table 1 below, which include data at long-term condition (2-8°C, inverted and upright), accelerated and stressed conditions.

**Table 1: Summary of Tables for JZP-458 Drug Product Stability Data**

| Batch       | Batch Number | Long-Term Storage Condition<br>Inverted | Long-Term Storage Condition<br>Upright | Accelerated Storage Condition    | Stress Storage Condition         |
|-------------|--------------|-----------------------------------------|----------------------------------------|----------------------------------|----------------------------------|
|             |              | 5°C ± 3°C                               | 5°C ± 3°C                              | 25°C ± 2°C,<br>60% RH ±<br>5% RH | 40°C ± 2°C,<br>75% RH ±<br>5% RH |
| PPQ 3       | AN9646       | Table 2                                 | N/A                                    | Table 3                          | Table 4                          |
| PPQ 2       | AN8391       | Table 5                                 | N/A                                    | Table 6                          | Table 7                          |
| PPQ 1       | AN8380       | Table 8                                 | N/A                                    | Table 9                          | Table 10                         |
| GMP 4       | AN8014       | Table 11                                | N/A                                    | Table 12                         | Table 13                         |
| GMP 3       | AM0383       | Table 14                                | N/A                                    | Table 15                         | Table 16                         |
| GMP 2       | AL4753       | Table 17                                | Table 18                               | Table 19                         | Table 20                         |
| GMP 1       | AK0926       | Table 21                                | Table 22                               | Table 23                         | Table 24                         |
| Engineering | 18C6003      | Table 25                                | Table 26                               | Table 27                         | Table 28                         |

N/A: Not Applicable

*Assessor comments:*

- All results at 2-8°C storage condition for DP GMP3 batch met the specifications up to 9 months; GMP1 and engineering batches met the specifications up to 24 months and no trends were observed.
- Particulate matter (b) (4) m increased overtime at long-term, accelerated, and stressed conditions for the engineering batch (b) (4) This batch formulation lacked PS80 and is not representative of commercial/clinical batches.
- Charge variants results by CIEX-UHPLC show a significant decrease in main peak and significant increases in acidic peak and basic peaks under accelerated and stress storage conditions. A decrease in main peak and an increase in minor peaks by RP-UHPLC were observed under accelerated and stressed conditions.
- Slight changes in purity by CIEX-UHPLC and RP-UHPLC were observed for uncovered DP vials exposed to light. Cartons of commercial packaging protected the DP from light.
- Overall, the DP is stable, and no trend was observed at long-term condition. The stability profile for all batches except for the engineering batch (higher subvisible particles) was similar under accelerated and stressed condition. The data from engineering batch at long-term condition are comparable with DP GMP1 and GMP2 batches. Therefore, it was appropriate to use GMP1, GMP2 and engineering batches stability data to set stability specification acceptance criteria.

## A. Appendices Table of Contents

**3.2.A.2 Adventitious Agents Safety Evaluation.** *The risk from adventitious agents is minimal as this is a manufacturing process with bacterial culture and no materials of animal or human origin were used in the manufacturing process. Viral clearance studies are not needed for products manufactured in bacteria.*

**3.2.R Regional Information:** Section 3.2.R contains copies of master batch records and executed batch records for three DS PPQ and three DP PPQ batches, tabulated list of DS and DP process controls, additional batch characterization data, analytical method validation report, DS and DP shipping protocols, and validation master plans and PPQ reports.

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Mekonnen  
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Dechassa

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Susan  
Kirshner

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## PRODUCT QUALITY FACILITY ASSESSMENT

### Memorandum of Review to the File

|                             |                                                                                                                                                     |
|-----------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Application ID</b>       | BLA 761179                                                                                                                                          |
| <b>Submission Type</b>      | Original BLA                                                                                                                                        |
| <b>Drug Product Name</b>    | asparaginase erwinia chrysanthemi (recombinant) (JZP-458)                                                                                           |
| <b>Strengths</b>            | 20 mg/mL                                                                                                                                            |
| <b>Dosage Form</b>          | Sterile solution for injection                                                                                                                      |
| <b>Administration Route</b> | IM injection                                                                                                                                        |
| <b>Indication</b>           | Treatment of ALL and LBL in adult and pediatric patients who have developed hypersensitivity or silent inactivation to E. coli-derived asparaginase |
| <b>Applicant Name</b>       | Jazz Pharmaceuticals Ireland Limited                                                                                                                |
| <b>US License Number</b>    | 2167                                                                                                                                                |
| <b>Application Type</b>     | 351 (a)                                                                                                                                             |
| <b>Primary Reviewer</b>     | Michael Shanks                                                                                                                                      |
| <b>Secondary Reviewer</b>   | Virginia Carroll                                                                                                                                    |
| <b>Goal Date</b>            | 10/30/2021                                                                                                                                          |

### Recommendation for Approvability:

- Manufacturing Facility Assessment Recommendation: Approval
- Product quality aspects not related to microbial control and facilities should be reviewed by OBP.

### Summary Basis of Recommendation (DS and DP):

Adequate descriptions of the facilities, equipment, environmental controls, cleaning and contamination control strategy were provided for (b) (4), proposed for Drug Substance (DS) and Drug Product (DP) manufacture, respectively. All proposed manufacturing and testing facilities are acceptable based on their current CGMP compliance status and recent relevant inspectional coverage.

A pre-license inspection of (b) (4) was conducted from (b) (4) by CDER/OPQ that resulted in a two-item FDA Form 483 with a final compliance recommendation of approve for BLA 761179. An OPMA/OBP decision to waive the DP PLI at (b) (4) was made based on the site's history.

### List Submissions being assessed (Table):

| Document Description (SD #) | Date Received |
|-----------------------------|---------------|
| BLA-761179-ORIG (0001)      | 12/09/2020    |
| BLA-761179-ORIG (0002)      | 12/10/2020    |
| BLA-761179-ORIG (0003)      | 12/18/2020    |
| BLA-761179-ORIG (0004)      | 01/13/2021    |
| BLA-761179-ORIG (0007)      | 02/19/2021    |

|                        |            |
|------------------------|------------|
| BLA-761179-ORIG (0015) | 03/11/2021 |
| BLA-761179-ORIG (0017) | 03/15/2021 |
| BLA-761179-ORIG (0022) | 03/30/2021 |
| BLA-761179-ORIG (0025) | 04/30/2021 |
| BLA-761179-ORIG (0045) | 06/15/2021 |
| BLA-761179-ORIG (0049) | 06/21/2021 |

## List of DMFs assessed (Table):

| DMF # | Date Reviewed | Finding | Document Reference |
|-------|---------------|---------|--------------------|
| N/A   | N/A           | -       | -                  |

## MODULE 3.2.S

### Module 3.2.S Lifecycle Management Considerations

|                           |    |
|---------------------------|----|
| Lifecycle considerations: | No |
| Post-approval inspection? | No |

## S.1 General Information

(b) (4) is responsible for the production of DS, analytical, release and stability DS testing, storage of Master and Working Cell Banks, and release and stability testing of commercial DP.

The manufacture of JZP-458 Drug Substance (DS) is performed in two main stages, upstream production and downstream purification in Building (b) (4)

JZP-458 is produced as an intracellular product in a *Pseudomonas fluorescens* cell line. (b) (4)

(b) (4) is responsible for production of DP, analytical, release and stability DP testing, and secondary packaging and labeling.

JZP-458 DP is manufactured under cGMP on (b) (4)

The DP manufacturing process is comprised of

(b) (4)

*Reviewer's Comment: For Information*

## S.2 Manufacture

### S.2.1 Manufacturer(s)

| Facility name and address | FEI     | Responsibilities and profile code(s)                                                                              |
|---------------------------|---------|-------------------------------------------------------------------------------------------------------------------|
| (b) (4)                   | (b) (4) | Production of Drug Substance, Analytical, Release and Stability testing, Storage of Master and Working Cell Banks |
|                           |         | CBI                                                                                                               |
|                           |         | Production and Initial Storage of the Master and Working Cell Banks                                               |
|                           |         | CBI                                                                                                               |
|                           |         | Drug Substance Enzyme Kinetics Assay                                                                              |
|                           |         | LCP                                                                                                               |
|                           |         | Storage of Master and Working Cell Banks                                                                          |
| (b) (4)                   | (b) (4) | CBI                                                                                                               |
|                           |         | Release of Commercial Drug Substance                                                                              |
| (b) (4)                   | (b) (4) | CBI SVS                                                                                                           |

*Reviewer's Evaluation:* The description of the DS manufacturing and testing facilities was adequate.

*Assessment:* SATISFACTORY

## MODULE 3.2.P

### Module 3.2.P Lifecycle Management Considerations

|                           |    |
|---------------------------|----|
| Lifecycle considerations: | No |
| Post-approval inspection? | No |

## P.1 Description and Composition of the Drug Product

JZP-458 drug product (DP) is a sterile liquid for intramuscular administration. Each single-use vial contains 10 mg of JZP-458, 0.5 mL nominal fill.

The DP is comprised of 20 mg/mL JZP-458 in 170 mM trehalose, 50 mM sodium chloride, 20 mM sodium phosphate buffer, 0.02% w/v polysorbate 80, pH 7.0.

*Reviewer's Comment: For Information*

## **P.3 Manufacture**

### **P.3.1 Manufacturer(s)**

(b) (4)



**U.S. FOOD & DRUG  
ADMINISTRATION**

Center for Drug Evaluation and Research  
Office of Pharmaceutical Quality  
Office of Biotechnology Products

**LABELS AND LABELING ASSESSMENT**

|                                 |                                                                                                                                                                                                            |
|---------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Date of Assessment:             | June 30, 2021                                                                                                                                                                                              |
| Assessor:                       | Vicky Borders-Hemphill, PharmD<br>Labeling Assessor<br>Office of Biotechnology Products (OBP)                                                                                                              |
| Through:                        | Mekonnen LemmaDechassa, PhD, Product Quality Assessor<br>Zhenzhen Liu, PhD, Product Quality Team Leader<br>OBP/Division of Biotechnology Review and Research 3                                             |
| Application:                    | BLA 761179                                                                                                                                                                                                 |
| Applicant:                      | Jazz Pharmaceuticals Ireland Limited                                                                                                                                                                       |
| Submission Date:                | December 9, 2020                                                                                                                                                                                           |
| Product:                        | Rylaze (asparaginase erwinia chrysanthemi (recombinant)-rywn)                                                                                                                                              |
| Dosage form(s):                 | Injection                                                                                                                                                                                                  |
| Strength and Container-Closure: | 10 mg/0.5 mL in a single-dose vial                                                                                                                                                                         |
| Purpose of assessment:          | The Applicant submitted a biologics license application for Agency assessment                                                                                                                              |
| <b>Recommendations:</b>         | The Prescribing Information (submitted on June 30, 2021), and container labels and carton labeling (submitted on June 17, 2021) were assessed and found to be acceptable from an OBP labeling perspective. |

| <b>Materials Considered for this Label and Labeling Assessment</b> |                         |
|--------------------------------------------------------------------|-------------------------|
| <b>Materials Assessed</b>                                          | <b>Appendix Section</b> |
| Proposed Labels and Labeling                                       | A                       |
| Evaluation Tables                                                  | B                       |
| Acceptable Labels and Labeling                                     | C                       |

n/a = not applicable for this assessment

**DISCUSSION**

We assessed the proposed labels and labeling for compliance with applicable requirements in the Code of Federal Regulations. Also, we assessed the proposed labels and labeling for consistency with recommended labeling practices. (see Appendix B)

**CONCLUSION**

The Prescribing Information (submitted on June 30, 2021), and container labels and carton labeling (submitted on June 17, 2021) were assessed and found to be acceptable (see Appendix C) from an OBP labeling perspective.

## **APPENDICES**

### **Appendix A:** Proposed Labeling

Prescribing Information (submitted on March 15, 2021

[\\CDSESUB1\evsprod\bla761179\0017\m1\us\jzp-458\\_nda-label-252550mg\\_vx0\\_15mar21\\_clean.docx](\\CDSESUB1\evsprod\bla761179\0017\m1\us\jzp-458_nda-label-252550mg_vx0_15mar21_clean.docx))

Medication Guide (N/A)

Instructions for Use (N/A)

Container Labels (submitted on March 15, 2021)

(b) (4)

**Appendix B: Evaluation Tables**  
**Evaluation Tables:** Label<sup>1,2</sup> and Labeling<sup>3</sup> Standards

**Container<sup>4</sup> Label Evaluation**

| <b><u>Proper Name (container label)</u></b>                                                                                                                                                     | <b><u>Acceptable</u></b>                                                                               |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulations: 21 CFR 610.60(a)(1), 21 CFR 201.10(g)(2), 21 CFR 610.62(a), 21 CFR 610.62(b), 21 CFR 610.62(c), 21 CFR 610.60(c), 21 CFR 201.50(b), 21 CFR 201.10(a), 21 CFR 201.10(h)(2)(i)(1)(i) | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |
| <i>Recommended labeling practices (placement of dosage form outside of parenthesis and/or below the proper name)</i>                                                                            | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

**Comment/Recommendation:** In response to OND review division requesting applicant provide justification for not revising the proper name to appear with no italics and no capitalization, the Applicant agreed to this revision in a communication dated 11Jun21.

<sup>1</sup> Per 21 CFR 1.3(b) *Label* means any display of written, printed, or graphic matter on the immediate container of any article, or any such matter affixed to any consumer commodity or affixed to or appearing upon a package containing any consumer commodity.

<sup>2</sup> Per CFR 600.3(dd) *Label* means any written, printed, or graphic matter on the container or package or any such matter clearly visible through the immediate carton, receptacle, or wrapper.

<sup>3</sup> Per 21 CFR 1.3(a) *Labeling* includes all written, printed, or graphic matter accompanying an article at any time while such article is in interstate commerce or held for sale after shipment or delivery in interstate commerce.

<sup>4</sup> Per 21 CFR 600.3(bb) *Container* (referred to also as "final container") is the immediate unit, bottle, vial, ampule, tube, or other receptacle containing the product as distributed for sale, barter, or exchange.

| <b>Manufacturer name, address, and license number (container label)</b>                                               | <b>Acceptable</b>                                                                                      |
|-----------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulations: 21 CFR 610.60(a)(2), 21 CFR 201.1(a), 21 CFR 610.60(c), 21 CFR 201.10(h)(2)(i)(1)(iv), 21 CFR 201.100(e) | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |
| <i>Recommended labeling practices (using the qualifying phrase "Manufactured by:")</i>                                | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |
| <i>Recommended labeling practices (U.S license number for container bearing a partial label<sup>5</sup>)</i>          | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

**Comment/Recommendation:** The name of the manufacturer, which is the license applicant listed in form FDA 356h as "Jazz Pharmaceuticals Ireland Limited", must appear on the container label (see 21 CFR 610.60(c)). Include a placeholder for the US License Number as follows:

Jazz Pharmaceuticals Ireland Limited

U.S. License No. xxxx

*Applicant revised as requested*

The distributor may be listed if the manufacturer name appears on the container label and space permits

| <b>Lot number or other lot identification (container label)</b>                                                         | <b>Acceptable</b>                                                                                      |
|-------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulations: 21 CFR 610.60(a)(3), 21 CFR 610.60(c), 21 CFR 201.18, 21 CFR 201.100(b)(6), 21 CFR 201.10(h)(2)(i)(1)(iii) | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

| <b>Expiration date (container label)</b>                                                                                                                                                                                                                                                                       | <b>Acceptable</b>                                                                                      |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulations: 21 CFR 610.60(a)(4), 21 CFR 201.17                                                                                                                                                                                                                                                                | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |
| <i>Recommended labeling practices references: USP General Chapters &lt;7&gt; Labeling, Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 lines 178-184, which, when finalized, will represent FDA's current thinking on topic</i> | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

<sup>5</sup> Per 21 CFR 610.60(c) *Partial Label*. If the container is capable of bearing only a partial label, the container shall show as a minimum the name (expressed either as the proper or common name), the lot number or other lot identification and the name of the manufacturer; in addition, for multiple dose containers, the recommended individual dose. Containers bearing partial labels shall be placed in a package which bears all the items required for a package label."

| <b>Beyond Use Date (Multiple-dose containers) (container label)</b>                                                                | <b>Acceptable</b>                                                                                      |
|------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| <i>Recommended labeling practices: USP General Chapters: &lt;659&gt; Packaging and Storage Requirements and &lt;7&gt; Labeling</i> | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |

| <b>Product Strength (container label)</b>                                                                                                                                                                                                                                                                                                               | <b>Acceptable</b>                                                                                      |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulations: 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)                                                                                                                                                                                                                                                                                                  | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |
| <i>Recommended labeling practices (expression of strength for injectable drugs) references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 line 176, which, when finalized, will represent FDA's current thinking on topic USP General Chapters: &lt;7&gt; Labeling</i> | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

|                                                                                                                                                |
|------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Comment/Recommendation:</b> Remove "per vial" from the strength statement for space considerations<br><i>Applicant revised as requested</i> |
|------------------------------------------------------------------------------------------------------------------------------------------------|

| <b>Multiple-dose containers (container label)</b>                                       | <b>Acceptable</b>                                                                                      |
|-----------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulations: 21 CFR 610.60(a)(5), 21 CFR 201.55<br><i>(recommended individual dose)</i> | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |

| <b>Statement: "Rx only" (container label)</b>                                                                                                                                                                                                                                                     | <b>Acceptable</b>                                                                                      |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulations: 21 CFR 610.60(a)(6), 21 CFR 201.100(b)(1)                                                                                                                                                                                                                                            | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |
| <i>Recommended labeling practices (prominence of Rx Only statement) reference: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 line 147, which, when finalized, will represent FDA's current thinking on topic</i> | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

| <b>Medication Guide (container label)</b>          | <b>Acceptable</b>                                                                                      |
|----------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulations: 21 CFR 610.60(a)(7), 21 CFR 208.24(d) | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |

| <b>No Package for container (container label)</b> | <b>Acceptable</b>                                                                                      |
|---------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulation: 21 CFR 610.60(b)                      | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |

| <b>No container label (container label)</b> | <b>Acceptable</b>                                                                                      |
|---------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulation: 21 CFR 610.60(d)                | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |

| <b>Ferrule and cap overseal (for vials only)</b>                                                                                                     | <b>Acceptable</b>                                                                                      |
|------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| <i>Recommended labeling practices references: United States Pharmacopeia (USP) General Chapters: &lt;7&gt; Labeling (Ferrules and Cap Overseals)</i> | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

|                                                                                                                                                                                                                               |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p><b>Comment/Recommendation:</b> Confirm there is no text on the ferrule and cap overseal of the vials.</p> <p><i>Applicant's response: Jazz confirms there is no text on the ferrule and cap overseal of the vials.</i></p> |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

| <b>Visual inspection</b>     | <b>Acceptable</b>                                                                                      |
|------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulation: 21 CFR 610.60(e) | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p><b>Comment/Recommendation:</b> Confirm that sufficient area of the container remains uncovered for its full length or circumference to allow for visual inspection when the label is affixed to the container and indicate where the visual area of inspection is located</p> <p><i>Applicant's response: Jazz confirms that the vial label dimensions and placement on the vial were developed to permit unobstructed visibility of the product following application of the label on the vial. The area of visual inspection is located vertically along the full length of the vial where the leading edge and trailing edge of the label leave an unobstructed area to view the vial contents.</i></p> <ul style="list-style-type: none"> <li><i>• Vial circumference is 50.27 mm (OD = 16 mm)</i></li> <li><i>• Label length = 44.45 mm</i></li> <li><i>• Gap = 5.82 mm (0.23")</i></li> </ul> <p><i>The label dimensions also permit visibility of the drug product horizontally:</i></p> <ul style="list-style-type: none"> <li><i>• Vial body height = 22 mm;</i></li> <li><i>• Label height = 15.87 mm;</i></li> <li><i>• Gap = 6.13mm (0.24") shared above and below the label.</i></li> </ul> |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

| <b>Route of administration (container label)</b>                                                                                                | <b>Acceptable</b>                                                                                      |
|-------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulations: 21 CFR 201.5(f), 21 CFR 201.100(b)(3), 21 CFR 201.100(d)(1)                                                                        | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |
| <i>Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)</i> | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

| <b>NDC numbers (container label)</b>     | <b>Acceptable</b>                                                                                      |
|------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulations: 21 CFR 201.2, 21 CFR 207.35 | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

| <b>Preparation instructions (container label)</b>                                                                                                                                                                                                            | <b>Acceptable</b>                                                                                      |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulation: 21 CFR 201.5(g)                                                                                                                                                                                                                                  | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |
| <i>Recommended labeling practices: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 426-430), which, when finalized, will represent FDA's current thinking on topic</i> | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |

| <b>Package type term (container label)</b>                                                                                                                                                                                                                                                                                                             | <b>Acceptable</b>                                                                                      |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| <i>Recommended labeling practices: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018)</i><br><i>USP chapter &lt;659&gt; Packaging and Storage Requirements</i> | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |

|                                                             |
|-------------------------------------------------------------|
| <b>Comment/Recommendation:</b> partial label considerations |
|-------------------------------------------------------------|

| <b>Misleading statements (container label)</b> | <b>Acceptable</b>                                                                                      |
|------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulation: 21 CFR 201.6                       | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |

| <b>Prominence of required label statements (container label)</b> | <b>Acceptable</b>                                                                                      |
|------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulation: 21 CFR 201.15                                        | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

| <b>Spanish-language (Drugs) (container label)</b> | <b>Acceptable</b>                                                                                      |
|---------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulation: 21 CFR 201.16                         | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |

| <b>FD&amp;C Yellow No. 5 and/or FD&amp;C Yellow No. 6 (container label)</b> | <b>Acceptable</b>                                                                                      |
|-----------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulation: 21 CFR 201.20                                                   | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |

| <b>Bar code label requirements (container label)</b>                                                                                                                                                                                                                                                                                                                                                  | <b>Acceptable</b>                                                                                      |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulations: 21 CFR 201.25, 21 CFR 610.67                                                                                                                                                                                                                                                                                                                                                             | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |
| <i>Recommended labeling practices references: Guidance for Industry: Bar Code Label Requirements Questions and Answers, August 2011</i><br><i>Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 511-512), lines 780-786), which, when finalized, will represent FDA's current thinking on topic</i> | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

| <b>Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products) (container label)</b> | <b>Acceptable</b>                                                                                      |
|-------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulations: 21 CFR 610.68, 21 CFR 201.26                                                                                           | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |

| <b>Net quantity (container label)</b>                                                                                                                                                                                                                                    | <b>Acceptable</b>                                                                                      |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulation: 21 CFR 201.51                                                                                                                                                                                                                                                | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |
| <i>Recommended labeling practices references: Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (line 461- 463) which, when finalized, will represent FDA's current thinking on topic</i> | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

|                                                                                                                                                                                                                                                               |  |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|
| <i>Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products Guidance for Industry, June 2015 (line 68, 93-99)</i><br><i>USP General Chapters &lt;1151&gt; Pharmaceutical Dosage Forms (Excess volume in injections).</i> |  |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|

| <b>Statement of Dosage (container label)</b>                                            | <b>Acceptable</b>                                                                                      |
|-----------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulations: 21 CFR 610.60(a)(5), 21 CFR 610.60(c), 21 CFR 201.55, 21 CFR 201.100(b)(2) | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

|                                                                                                                                                                   |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Comment/Recommendation:</b> Consider revising to read: "Dosage: See Prescribing Information" for space considerations<br><i>Applicant revised as requested</i> |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------|

| <b>Inactive ingredients (container label)</b>                                                                                                                   | <b>Acceptable</b>                                                                                      |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulation: 21 CFR 201.100                                                                                                                                      | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |
| <i>Recommended labeling practices reference: USP General Chapters &lt;1091&gt; Labeling of Inactive Ingredients and USP General Chapters &lt;7&gt; Labeling</i> | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |

| <b>Storage requirements (container label)</b>                                                                                                                  | <b>Acceptable</b>                                                                                      |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| <i>Recommended labeling practices references: USP General Chapters &lt;7&gt; Labeling, USP General Chapters &lt;659&gt; Packaging and Storage Requirements</i> | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

| <b>Dispensing container (container label)</b> | <b>Acceptable</b>                                                                                      |
|-----------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulation: 21 CFR 201.100(b)(7)              | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |

### **Package<sup>6</sup> Labeling Evaluation**

| <b>Proper name (package labeling)</b>                                                                                | <b>Acceptable</b>                                                                                      |
|----------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulations: 21 CFR 610.61(a), 21 CFR 201.50(b), 21 CFR 201.10(g)(2)                                                 | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |
| <i>Recommended labeling practices (placement of dosage form outside of parenthesis and/or below the proper name)</i> | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

| <b>Manufacturer name, address, and license number (package labeling)</b>               | <b>Acceptable</b>                                                                                      |
|----------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulations: 21 CFR 610.61(b), 21 CFR 201.1(a), 21 CFR 201.1(i), 21 CFR 201.100(e)     | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |
| <i>Recommended labeling practices (using the qualifying phrase "Manufactured by:")</i> | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

**Comment/Recommendation:** The name of the manufacturer, which is the license applicant listed in form FDA 356h as "Jazz Pharmaceuticals Ireland Limited", must appear on the carton labeling. Include a placeholder for the US License Number as follows:  
Manufactured by: Jazz Pharmaceuticals Ireland Limited  
Leinster, Ireland  
U.S. License No. xxxx  
*Applicant revised as requested*

| <b>Lot number or other lot identification (package labeling)</b> | <b>Acceptable</b>                                                                                      |
|------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulation: 21 CFR 610.61(c), 21 CFR 201.18                      | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

| <b>Expiration date (package labeling)</b>    | <b>Acceptable</b>                                                                                      |
|----------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulations: 21 CFR 610.61(d), 21 CFR 201.17 | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

<sup>6</sup> Per 21 CFR 600.3(cc) *Package* means the immediate carton, receptacle, or wrapper, including all labeling matter therein and thereon, and the contents of the one or more enclosed containers. If no package, as defined in the preceding sentence, is used, the container shall be deemed to be the package. Thus, this includes the carton, prescribing information, and patient labeling.

| <b>Beyond Use Date (Multiple-dose containers) (package labeling)</b>                                                               | <b>Acceptable</b>                                                                                      |
|------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| <i>Recommended labeling practices: USP General Chapters: &lt;659&gt; Packaging and Storage Requirements and &lt;7&gt; Labeling</i> | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |

| <b>Preservative (package labeling)</b> | <b>Acceptable</b>                                                                                      |
|----------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulation: 21 CFR 610.61(e)           | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

| <b>Number of containers (package labeling)</b> | <b>Acceptable</b>                                                                                      |
|------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulation: 21 CFR 610.61(f)                   | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

| <b>Product Strength (package labeling)</b>                                                                                                                                                                                                                                                                      | <b>Acceptable</b>                                                                                      |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulations: 21 CFR 610.61(g), 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)                                                                                                                                                                                                                                        | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |
| <i>Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (line 176), which, when finalized, will represent FDA's current thinking on topic<br/>USP General Chapters: &lt;7&gt; Labeling</i> | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

| <b>Storage temperature/requirements (package labeling)</b>                                                                                                     | <b>Acceptable</b>                                                                                      |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulation: 21 CFR 610.61(h)                                                                                                                                   | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |
| <i>Recommended labeling practices reference: USP General Chapters: &lt;7&gt; Labeling, USP General Chapters &lt;659&gt; Packaging and Storage Requirements</i> | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

| <b>Handling: "Do Not Shake", "Do not Freeze" or equivalent (package labeling)</b> | <b>Acceptable</b>                                                                                      |
|-----------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulation: 21 CFR 610.61(i)                                                      | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

| <b>Multiple dose containers (recommended individual dose) (package labeling)</b> | <b>Acceptable</b>                                                                                      |
|----------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulation: 21 CFR 610.61(j)                                                     | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |

| <b>Route of administration (package labeling)</b>                                                                                               | <b>Acceptable</b>                                                                                      |
|-------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulations: 21 CFR 610.61(k), 21 CFR 201.5(f), 21 CFR 201.100(d)(1)                                                                            | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |
| <i>Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)</i> | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

| <b>Known sensitizing substances (package labeling)</b>                                                | <b>Acceptable</b>                                                                                      |
|-------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulations: 21 CFR 610.61(l), 21 CFR 801.437 (User labeling for devices that contain natural rubber) | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |

| <b>Inactive ingredients (package labeling)</b>                                                                                                                | <b>Acceptable</b>                                                                                      |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulations: 21 CFR 610.61, 21 CFR 201.100                                                                                                                    | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |
| <i>Recommended labeling practices references: USP General Chapters &lt;1091&gt; Labeling of Inactive Ingredients, USP General Chapters &lt;7&gt; Labeling</i> | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Comment/Recommendation:</b><br>Revised the ingredient list as follows to include the net quantity, to revise the inactive ingredients in alphabetical order, and to name the inactive ingredients per 3.2.P.1 submission to the BLA: "Each 0.5 mL contains 10 mg asparaginase Erwinia chrysanthemi (recombinant)-xxxx and the inactive ingredients: polysorbate 80 (0.1 mg), sodium chloride (1.5 mg), sodium phosphate dibasic anhydrous (0.8 mg), sodium phosphate monobasic monohydrate (0.6 mg), and trehalose (32.1 mg). Sodium chloride may be added to adjust the pH. The pH is approximately 7."<br><i>Applicant revised as requested</i> |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

| <b>Source of the product (package labeling)</b> | <b>Acceptable</b>                                                                                      |
|-------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulation: 21 CFR 610.61(p)                    | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |

| <b>Minimum potency of product (package labeling)</b> | <b>Acceptable</b>                                                                                      |
|------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulation: 21 CFR 610.61(r)                         | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

| <b>Rx only (package labeling)</b>                                                                                                                                                                                                                                      | <b>Acceptable</b>                                                                                      |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulations: 21 CFR 610.61(s), 21 CFR 201.100(b)(1)                                                                                                                                                                                                                    | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |
| <i>Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (line 147-149), which, when finalized, will represent FDA's current thinking on topic</i> | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

| <b>Divided manufacturing (package labeling)</b>                              | <b>Acceptable</b>                                                                                      |
|------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulation: 21 CFR 610.63 (Divided manufacturing responsibility to be shown) | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |

| <b>Distributor (package labeling)</b>         | <b>Acceptable</b>                                                                                      |
|-----------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulation: 21 CFR 610.64, 21 CFR 201.1(h)(5) | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

| <b>Bar code (package labeling)</b>                                                                                                                                                                                                                                                                                       | <b>Acceptable</b>                                                                                      |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulations: 21 CFR 610.67, 21 CFR 201.25                                                                                                                                                                                                                                                                                | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |
| <i>Recommended labeling practices references: Guidance for Industry: Bar Code Label Requirements Questions and Answers, August 2011<br/>Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 511-512), lines 780-786)</i> | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

| <b><u>Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products) (package labeling)</u></b> | <b><u>Acceptable</u></b>                                                                               |
|---------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulations: 21 CFR 610.68, 21 CFR 201.26                                                                                                   | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |

| <b><u>NDC numbers (package labeling)</u></b> | <b><u>Acceptable</u></b>                                                                               |
|----------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulations: 21 CFR 201.2, 21 CFR 207.35     | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

| <b><u>Preparation instructions (package labeling)</u></b>                                                                                                                                                                                                                                                                 | <b><u>Acceptable</u></b>                                                                               |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulation: 21 CFR 201.5(g) and 21 CFR 610.61(i)                                                                                                                                                                                                                                                                          | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |
| <i>Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 426-430), which, when finalized, will represent FDA's current thinking on topic</i><br><i>USP General Chapters &lt;7&gt; Labeling</i> | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |

| <b><u>Package type term (package labeling)</u></b>                                                                                                                                                                                                                                                                                                     | <b><u>Acceptable</u></b>                                                                               |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| <i>Recommended labeling practices: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018)</i><br><i>USP chapter &lt;659&gt; Packaging and Storage Requirements</i> | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

| <b><u>Misleading statements (package labeling)</u></b> | <b><u>Acceptable</u></b>                                                                               |
|--------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulation: 21 CFR 201.6                               | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |

| <b><u>Prominence of required label statements (package labeling)</u></b> | <b><u>Acceptable</u></b>                                                                               |
|--------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulation: 21 CFR 201.15                                                | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

| <b>Spanish-language (Drugs) (package labeling)</b> | <b>Acceptable</b>                                                                                      |
|----------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulation: 21 CFR 201.16                          | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |

| <b>FD&amp;C Yellow No. 5 and/or FD&amp;C Yellow No. 6 (package labeling)</b> | <b>Acceptable</b>                                                                                      |
|------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulation: 21 CFR 201.20                                                    | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |

| <b>Phenylalanine as a component of aspartame (package labeling)</b> | <b>Acceptable</b>                                                                                      |
|---------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulation: 21 CFR 201.21(c)                                        | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |

| <b>Sulfites; required warning statements (package labeling)</b> | <b>Acceptable</b>                                                                                      |
|-----------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulation: 21 CFR 201.22(b)                                    | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |

| <b>Net quantity (package labeling)</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | <b>Acceptable</b>                                                                                      |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulation: 21 CFR 201.51                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |
| <i>Recommended labeling practices references: Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (line 461- 463) which, when finalized, will represent FDA's current thinking on topic</i><br><i>Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products Guidance for Industry, June 2015 (line 68, 93-99)</i><br><i>USP General Chapters &lt;1151&gt; Pharmaceutical Dosage Forms (Excess volume in injections).</i> | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

**Comment/Recommendation:** see ingredients list comment

| <b>Statement of Dosage (package labeling)</b>    | <b>Acceptable</b>                                                                                      |
|--------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulations: 21 CFR 201.55, 21 CFR 201.100(b)(2) | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

**Comment/Recommendation:** Consider revising to read: "Dosage: See Prescribing Information" to match your container label statement  
*Applicant revised as requested*

| <b>Dispensing container (package labeling)</b> | <b>Acceptable</b>                                                                                      |
|------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulation: 21 CFR 201.100(b)(7)               | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |

| <b>Medication Guide (package labeling)</b>         | <b>Acceptable</b>                                                                                      |
|----------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulations: 21 CFR 610.60(a)(7), 21 CFR 208.24(d) | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |

### **Prescribing Information Evaluation**

#### **PRESCRIBING INFORMATION**

| <b>Highlights of Prescribing Information</b>                                                                                                                                                                                                                                                                                        |                                                                                                        |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| <b>PRODUCT TITLE</b>                                                                                                                                                                                                                                                                                                                | <b>Acceptable</b>                                                                                      |
| Regulation: 21 CFR 201.57(a)(2)                                                                                                                                                                                                                                                                                                     | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |
| <i>Recommended labeling practices reference: Draft Guidance for Industry on Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products - Content and Format (January 2018), which, when finalized, will represent FDA's current thinking on topic</i> | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

**Comment/Recommendation:** Revise to lower case parenthetical "recombinant" across all labeling *Applicant revised as requested*

| <b>Highlights of Prescribing Information</b>                                                             |                                                                                                        |
|----------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| <b>DOSAGE AND ADMINISTRATION</b>                                                                         | <b>Acceptable</b>                                                                                      |
| <i>Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions</i> | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |

| <b>Highlights of Prescribing Information</b>                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                        |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| <b>DOSAGE FORMS AND STRENGTHS</b>                                                                                                                                                                                                                                                                                                                                                                                    | <b>Acceptable</b>                                                                                      |
| Regulations: 21 CFR 201.57(a)(8), 21 CFR 201.10, 21 CFR 201.100                                                                                                                                                                                                                                                                                                                                                      | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |
| <i>Recommended labeling practices references: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018)</i><br><i>USP chapter &lt;659&gt; Packaging and Storage Requirements</i><br><i>USP General Chapters: &lt;7&gt; Labeling</i> | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

**Comment/Recommendation:** We deleted the identifying characteristics from the Highlights Dosage Forms and Strengths since this section is to provide a concise summary of the full prescribing information Dosage Forms and Strengths *Applicant revised as requested*

| <b>Full Prescribing Information</b>                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                        |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| <b>2 DOSAGE AND ADMINISTRATION</b>                                                                                                                                                                                                                                                                                                                                                                                                                   | <b>Acceptable</b>                                                                                      |
| Regulation: 21 CFR 201.57(c)(3)(iv)]<br><i>Confirm appropriateness of specific direction on dilution, preparation, and administration of the dosage form and storage conditions for stability of the reconstituted or diluted drug; ensure verbatim statement for parenterals: "Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit."</i> | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |
| <i>Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions and storage instructions for reconstituted and diluted products; confirm the appropriateness of infusion bags, infusion sets (e.g., tubing, infusion aids, or filter membranes) incompatibilities with these components</i>                                                                                                                     | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |

**Comment/Recommendation:** We added "Administer RYLAZE immediately after drawing the dose into the syringe(s). Discard any unused RYLAZE remaining in a dosing syringe"

*Applicant revised as "Administer RYLAZE within 4 hours after drawing the dose into the syringe(s). The syringes should be stored at room temperature and do not need to be protected from light before use." Product quality and OPMA determine data supports this change.*

We recommend including temperature ranges for clarity as follows: "Administer RYLAZE by intramuscular injection within 4 hours after drawing the dose into the syringe(s). If needed, store the syringes at room temperature (15°C to 25°C [59°F to 77°F]) or refrigerated at 2°C

to 8°C (36°F to 46°F) for up to 4 hours. The syringe does not need to be protected from light during storage.”

*Applicant revised as requested*

| Full Prescribing Information                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                        |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| <b>3 DOSAGE FORMS AND STRENGTHS</b>                                                                                                                                                                                                                                                                                                                                                                                  | <b>Acceptable</b>                                                                                      |
| Regulation: 21 CFR 201.57(c)(4)                                                                                                                                                                                                                                                                                                                                                                                      | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |
| <i>Recommended labeling practices references: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018)</i><br><i>USP chapter &lt;659&gt; Packaging and Storage Requirements</i><br><i>USP General Chapters: &lt;7&gt; Labeling</i> | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

| Full Prescribing Information                                                                                        |                                                                                                        |
|---------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| <b>11 DESCRIPTION</b>                                                                                               | <b>Acceptable</b>                                                                                      |
| Regulations: 21 CFR 201.57(c)(12), 21 CFR 610.61 (m), 21 CFR 610.61(o), 21 CFR 610.61 (p), 21 CFR 610.61 (q)        | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |
| <i>Recommended labeling practices references: USP General Chapters &lt;1091&gt;, USP General Chapters &lt;7&gt;</i> | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

**Comment/Recommendation:** The proper name has replaced the placeholder for the tradename since the first paragraph discusses the drug substance *Applicant revised as requested*

No data was provided in the BLA to support that the structure, physicochemical properties of your product are comparable to crisantaspase. Therefore, the second half of this sentence “and the structure and physiochemical properties of the enzyme are consistent with those of the native asparaginase *Erwinia chrysanthemi* (also known as crisantaspase)” should not be included in the labeling until relevant data are reviewed by the Agency. Even with comparability data it is not determined that we would allow a statement regarding structural consistency with another product. *Applicant revised as requested*

We added the dosage form *Applicant revised as requested*

We revised the ingredient list as follows to include the net quantity, to revise the inactive ingredients in alphabetical order, and to name the inactive ingredients per 3.2.P.1 submission to the BLA *Applicant revised as requested*

| Full Prescribing Information                                                                                                                                                                                                                                                                                                                         |                                                                                                        |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| <b>15 &amp; 16 Hazardous Drug</b>                                                                                                                                                                                                                                                                                                                    | <b>Acceptable</b>                                                                                      |
| Regulation: 21 CFR 201.57(c)(17)(iv)<br><br>Section 15:<br>References 1. OSHA Hazardous Drugs. OSHA.<br><a href="http://www.osha.gov/SLTC/hazardousdrugs/index.html">http://www.osha.gov/SLTC/hazardousdrugs/index.html</a><br><br>Section 16:<br>xxxx is a hazardous drug. Follow applicable special handling and disposal procedures. <sup>1</sup> | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |

| Full Prescribing Information                                                                                                     |                                                                                                        |
|----------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| <b>16 HOW SUPPLIED/ STORAGE AND HANDLING</b>                                                                                     | <b>Acceptable</b>                                                                                      |
| Regulation: 21 CFR 201.57(c)(17)                                                                                                 | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |
| <i>Recommended labeling practices: to ensure placement of detailed storage conditions for reconstituted and diluted products</i> | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |

**Comment/Recommendation:** Provide the data to support this statement or delete:

" (b) (4)

The Applicant deleted.

(b) (4)

Delete the syringe storage information from section 16 since this information is really pertinent to instructions that should be conveyed for administration and preparation in the DOSAGE AND ADMINISTRATION section rather than the HOW SUPPLIED/STORAGE AND HANDLING section as it is not pertaining to the supplied product in vial.

The Applicant deleted

| Full Prescribing Information                                                                                                                                                                                                                                                                  |                                                                                                        |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| <b>MANUFACTURER INFORMATION</b>                                                                                                                                                                                                                                                               | <b>Acceptable</b>                                                                                      |
| Regulations: 21 CFR 201.100(e), 21 CFR 201.1                                                                                                                                                                                                                                                  | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |
| <i>Recommended labeling practices references: 21 CFR 610.61(b) (add the US license number for consistency with the carton labeling), and 21 CFR 610.64 (Name and address of distributor may appear and use a qualifying phrase for consistency with the carton labeling, when applicable)</i> | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

**Comment/Recommendation:** We added the name and address of the manufacturer, which is the license applicant listed in form FDA 356h as "Jazz Pharmaceuticals Ireland Limited" and a placeholder for the US license number *Applicant revised as requested*

Medication Guide Evaluation (N/A)  
Patient Information Labeling Evaluation (N/A)  
Instructions for Use Evaluation (N/A)

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



Vicky  
Borders-Hemphill

Digitally signed by Vicky Borders-Hemphill  
Date: 6/30/2021 03:25:37PM  
GUID: 50814c7000007a3d59329f660d8ddf02



Zhenzhen  
Liu

Digitally signed by Zhenzhen Liu  
Date: 6/30/2021 03:39:08PM  
GUID: 555108d8007bb3724ef2a6d3413e2758