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STATISTICAL ANALYSIS PLAN

VERSION: 1.4
DATE: 16-DEC-2020

STUDY DRUG:

Recombinant Crisantaspase *Pseudomonas fluorescens* (RC-P), JZP-458

PROTOCOL/STUDY NUMBER:

JZP458-201 Protocol original version (29 August 2019)

Amendment 01 (18 August 2020)

Amendment 02 (03 September 2020)

STUDY TITLE:

An Open-Label, Multicenter Study of RC-P in Patients with Acute Lymphoblastic Leukemia (ALL)/Lymphoblastic Lymphoma (LBL) Following Hypersensitivity to *E. coli*-derived *Asparaginases*

SPONSOR (UNITED STATES REPRESENTATIVE):

Jazz Pharmaceuticals

3170 Porter Dr, Palo Alto, CA 94304

This study is being conducted in compliance with good clinical practice, including the archiving of essential documents.

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1. LIST OF ABBREVIATIONS

Table 1: List of Abbreviations

Abbreviation	Term
ADA	Anti-drug antibody
AE	Adverse event
ALL	Acute lymphoblastic leukemia
BSA	Body surface area
CI	Confidence interval
COG	Children's Oncology Group
CSR	Clinical study report
CTCAE	Common terminology criteria for adverse events
CV	Coefficient of variation
E. coli	*Escherichia coli*
eCRF	Electronic case report form
EDC	Electronic data capture
FDA	Food and Drug Administration
ICH	International Council for Harmonisation
IM	Intramuscular
IU	International unit(s)
LBL	Lymphoblastic lymphoma
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
NSAA	Nadir serum asparaginase activity
PD	Pharmacodynamics
PK	Pharmacokinetic
PT	Preferred term
RC-P	Recombinant crisantaspase produced in *Pseudomonas fluorescens*
SAA	Serum asparaginase activity
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SDRC	Study data review committee
SOC	System organ class

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SOP	Standard operating procedures
TEAE	Treatment emergent adverse event
WHO	World Health Organization

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2. MODIFICATION HISTORY

Version History for SAP:

Version	Date	Description
1.0	18DEC2019	Original
1.1	07APR2020	Clarification on the Efficacy/PK/PD Analysis Sets and sample size at the interim analysis in Section 5.3
1.2	08JUN2020	Further clarification and language update on the sample size at the interim analysis in Section 5.3
1.3	24SEP2020	• Update study design in Section 5 per protocol amendment 1 and 2. • Clarification on the sample size at the primary analysis in Section 5.3. • Addition of the sensitivity analyses to assess COVID-19 impact on the primary (Section 9.1.3) and key secondary (Section 9.2.3) efficacy endpoints. • Addition of Section 13. COVID-19
1.4	16DEC2020	• Added the term of pulmonary embolism to the list of preferred terms for the AE of special interest of thrombosis.

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3. INTRODUCTION

This is an open-label, multicenter, dose confirmation, and pharmacokinetic (PK) study of Recombinant Crisantaspase Produced in *Pseudomonas fluorescens* (RC-P) in patients (of any age) with acute lymphoblastic leukemia (ALL)/lymphoblastic lymphoma (LBL) who are hypersensitive to *E. coli*-derived asparaginases (allergic reaction or silent inactivation).

This study has *i*) one interim analysis which is planned after the 51st patient completes Course 1 at the final intramuscular (IM) RC-P dose in Part A (Cohorts 1 and 2), *ii*) one primary analysis which is planned after the 98th patient completes Course 1 at the final IM RC-P dose in Part A (Cohorts 1 and 2), and *iii*) the final analysis which is planned when the overall study (Part A and Part B) is complete and all enrolled patients have completed all of their planned courses of RC-P, including end of study procedures, or have discontinued the study early.

The purpose of this statistical analysis plan (SAP) is to describe in detail the statistical methodology and planned analyses to be conducted for the interim, primary and final analysis of Protocol JZP458-201 for inclusion in the Clinical Study Report (CSR). The current version is based on Protocol amendment 02 dated 03 September 2020. Any additional analyses or deviation from the analyses outlined in this plan will be documented with rationale in the final clinical study report (CSR).

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4. STUDY OBJECTIVES AND ENDPOINTS

4.1. Study Objectives

4.1.1. Primary Objectives

The primary objectives of the study are as follows:

- To determine the efficacy of intramuscular (IM) RC-P administration as measured by the response in Cohort 1 and Cohort 2, defined as the last 72-hour nadir serum asparaginase activity (NSAA) level ≥ 0.1 IU/mL during the first course
- To assess the safety and tolerability of IM RC-P in patients with ALL/LBL who are hypersensitive to *E. coli*-derived asparaginases

4.1.2. Secondary Objective

4.1.2.1. Key Secondary Objective

The key secondary objective of the study is to determine the efficacy of IM RC-P administration as measured by the response in Cohort 1 and Cohort 2, defined as the last 48-hour NSAA level ≥ 0.1 IU/mL during the first course.

4.1.2.2. Secondary Objectives

Other secondary objectives of the study are as follows:

- To determine the efficacy of IM RC-P administration as measured by the response in Cohort 1 and Cohort 2, defined as the last 48-hour and the last 72-hour NSAA levels ≥ 0.4 IU/mL during the first course
- To characterize the pharmacokinetics (PK) of IM RC-P using a population PK approach, and to explore exposure-response correlations
- To assess the immunogenicity of IM RC-P following repeat administration of RC-P

4.1.3. Exploratory Objectives

The exploratory objectives of this study are as follows:

- To determine the efficacy of intravenous (IV) RC-P administration as measured by the response, defined as the last 48-hour NSAA ≥ 0.1 IU/mL and the last 72-hour NSAA ≥ 0.1 IU/mL during the first course
- To determine the efficacy of IV RC-P administration measured by the response, defined as the last 48-hour NSAA ≥ 0.4 IU/mL and the last 72-hour NSAA ≥ 0.4 IU/mL during the first course
- To assess the safety and tolerability of IV RC-P in patients with ALL/LBL who are hypersensitive to *E. coli*-derived asparaginases
- To characterize the PK of IV RC-P using a population PK approach
- To assess the immunogenicity of IV RC-P following repeat administration of RC-P

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4.2. Study Endpoints

4.2.1. Primary Endpoints

- The primary efficacy endpoint of the study is the response rate, defined as the proportion of patients with the last 72-hour NSAA level ≥ 0.1 IU/mL during the first course of IM RC-P. Depending on the RC-P start day for a patient, this could be predose 4 if the first course of RC-P started on a Monday; predose 6 if the first course of RC-P started on a Wednesday; or predose 5 if the first course of RC-P started on a Friday.
- The primary safety endpoint of the study is the safety and tolerability of IM RC-P in patients with ALL/LBL who are hypersensitive to *E. coli*-derived asparaginases. This swill be determined by the occurrence of treatment-emergent adverse events.

4.2.2. Secondary Endpoints

4.2.2.1. Key Secondary Endpoint

- Proportion of patients with the last 48-hour NSAA level ≥ 0.1 IU/mL during the first course of IM administration of RC-P

4.2.2.2. Other Secondary Endpoints

Secondary endpoints for patients in Part A:

- Proportion of patients with the last 48-hour NSAA level ≥ 0.4 IU/mL during the first course of IM administration of RC-P
- Proportion of patients with the last 72-hour NSAA level ≥ 0.4 IU/mL during the first course of IM administration of RC-P
- Characterization of the PK of IM RC-P based on SAA using a population PK approach and exposure-response correlations
- Incidence of anti-drug antibody (ADA) formation against RC-P

4.2.3. Exploratory Endpoints

Exploratory endpoints for patients in Part B:

- Proportion of patients with the last 48-hour NSAA level ≥ 0.1 IU/mL during the first course of IV administration of RC-P
- Proportion of patients with the last 72-hour NSAA level ≥ 0.1 IU/mL during the first course of IV administration of RC-P
- Proportion of patients with the last 48-hour NSAA level ≥ 0.4 IU/mL during the first course of IV administration of RC-P
- Proportion of patients with the last 72-hour NSAA level ≥ 0.4 IU/mL during the first course of IV administration of RC-P
- Incidence of treatment emergent adverse events
- Characterization of the PK of IV RC-P based on SAA using a population PK approach

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- Incidence of ADA formation against RC-P

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5. STUDY DESIGN

5.1. Summary of Study Design

This study is designed to assess the tolerability and efficacy of RC-P (only in patients with ALL/LBL who develop hypersensitivity to an *E. coli*-derived asparaginase), as measured by asparaginase activity. In this patient population, 6 doses of RC-P should be substituted for each dose of a long-acting *E. coli*-derived asparaginase. Two consecutive weeks' treatment of RC-P is defined as one course. Additional courses of RC-P will be administered based on each patient's original treatment plan for as long as the patient derives clinical benefit.

This study will consist of two parts: **Part A** to determine the dose of RC-P for IM administration and to confirm safety and efficacy; and **Part B** to define the optimal dose and schedule of IV RC-P. Part A and Part B may be investigated in parallel.

Efficacy and safety data will be assessed by a Study Data Review Committee (SDRC) at frequent intervals as described below. The SDRC will make recommendations and have oversight of the study as described in the protocol and the SDRC Charter. The SDRC will review results throughout the study as follows: for Part A at n = 6 and 13 (for each Cohort 1 subcohort), at n = 19, 32, and 51 (Cohort 1 plus Cohort 2 at the final IM RC-P dose with n=51 as the interim analysis); and Part B at n = 6 at a minimum.

IM RC-P Dose Confirmation (Part A):

Part A (IM RC-P) of the study will have 2 IM cohorts:

- Cohort 1 (includes multiple subcohorts), an RC-P repeat dose/confirmatory cohort with the initial RC-P dose of 25 mg/m^2 based on data from the Phase 1 healthy subject study; a final IM RC-P dose level will be selected, and
- Cohort 2, an expansion cohort to confirm the efficacy and safety of the final IM RC-P dose level and schedule; a maximum target of 20% of the patients enrolled in Cohort 2 may enter the study based on a Grade 2 allergic reaction (Inclusion Criterion #3).

Part A Cohort 1 (IM Dose Confirmation): Patients in this cohort will be administered 6 doses of IM RC-P (Course 1), to evaluate the safety/tolerability and efficacy of repeated doses of IM RC-P. Cohort 1 patients will have 6 IM RC-P doses administered on a Monday, Wednesday, Friday (MWF) schedule over 2 weeks with the initial dose starting either on a Monday or Wednesday or Friday (depending on the patient's planned chemotherapy schedule). The starting dose for RC-P Dose Cohort 1a will be 25 mg/m^2. Additional subcohorts (eg, Cohort 1b, Cohort 1c…Cohort 1x) may be enrolled to determine the optimal dose for Cohort 2.

A target of 13 evaluable patients will be enrolled in each Cohort 1 subcohort. Evaluable patients for Cohort 1 are defined as patients who have received at least 3 doses of IM RC-P and have a 72-hour NSAA level (obtained within ± 2-hour window) during the second half of Course 1. For patients who are treated but are not evaluable, additional patients may be enrolled. Patients who discontinue RC-P will be evaluated for safety.

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The SDRC will review the data when 6 evaluable patients in each subcohort complete Course 1. If 6 of the 6 evaluable patients in that subcohort have a 72-hour NSAA level ≥ 0.1 IU/mL and the safety/tolerability issues are acceptable based on a review by the SDRC, then the SDRC will also review the data when 13 evaluable patients in each subcohort complete Course 1. If 13 of the 13 (100%) evaluable patients in that subcohort have 72-hour NSAA levels ≥ 0.1 IU/mL and the safety/tolerability issues are acceptable based on a review by the SDRC, no additional patients will be enrolled in Cohort 1. Patients will be enrolled at this IM RC-P dose level in Part A Cohort 2 of this study.

If 1 or more of the 13 evaluable patients in the subcohort has a 72-hour NSAA level < 0.1 IU/mL, or if any safety/tolerability issues are not acceptable based on a review by the SDRC, then the PK and safety data will be analyzed to determine whether a new subcohort (with a lower dose, higher dose, or different doses on different days) is needed. Based on all of the data, the SDRC may recommend that a different dose be given on Fridays than on Mondays and Wednesdays. Any additional dose level(s) studied for RC-P will not exceed a 50% increase from the previous dose level.

Part A Cohort 2 (IM Expansion): Approximately 85 patients are expected to be enrolled in this cohort and each patient is planned to receive at least 6 doses (1 course) of IM RC-P at the final IM RC-P dose level selected from Part A Cohort 1.

The SDRC will review the data on NSAA levels at frequent intervals for Cohort 2; these reviews will occur when totals of 19, 32, and 51 patients (Cohort 1 plus Cohort 2 at the final IM RC-P dose with n=51 as the interim analysis) complete Course 1. In addition, the SDRC will review the data to assess the safety of the selected dose level when 32 and 51 patients complete Course 1. Enrollment for this cohort may be stopped if the incidence of allergic reactions (including hypersensitivity and anaphylaxis) related to RC-P exceeds 25%, or the incidence of pancreatitis exceeds 10% or thrombosis exceeds 10%.

IV RC-P Dose Confirmation (Part B):

Part B (IV RC-P) may begin in parallel with Part A; study center participation will be at the discretion of the Sponsor. Part B of this study will be conducted to define the optimal dose of the IV administration of RC-P for further study in ALL/LBL patients as a repeated dose. Part B patients will have 6 IV RC-P doses administered on a MWF schedule over 2 weeks with the initial dose starting either on a Monday or Wednesday or Friday (depending on the patient's planned chemotherapy schedule).

Part B (IV RC-P) of the study will have at least 1 IV subcohort at a starting dose of 37.5 mg/m^2:

- Cohort 1 (may include multiple subcohorts), IV RC-P Dose Confirmation

Part B Cohort 1 (IV Dose Confirmation): RC-P to study IV administration in Part B Cohort 1 will be provided as 6 doses for each patient.

A target of at least 6 evaluable patients will be enrolled in Cohort 1a; more patients may be enrolled as described below. Evaluable patients for Cohort 1 are defined as patients who have received at least 3 doses of IV RC-P and have a 72-hour NSAA level (obtained within the ± 2-

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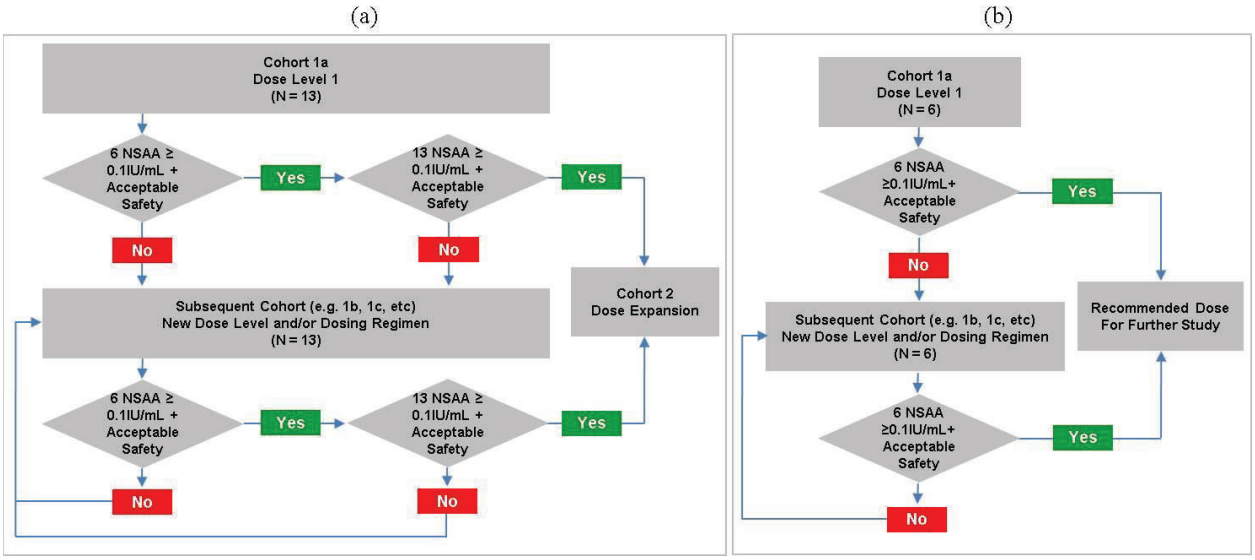
hour window) during the second half of Course 1. For patients who are treated but are not evaluable, additional patients may be enrolled.

If 6 of the 6 evaluable patients in Cohort 1a have a 72-hour NSAA level ≥ 0.1 IU/mL and the safety/tolerability issues are acceptable based on a review by the SDRC, the dose may be confirmed as a dose for further evaluation. If the dose is not confirmed, additional subcohorts may be investigated. The dose chosen for further evaluation may be used in a Part B IV expansion cohort of this study using a similar design as used in Part A Cohort 2, if the Sponsor determines that an IV Expansion Cohort 2 is to be done in this study (Figure 1b).

Figure 1: (a) Part A IM RC-P Dose Cohorts; (b) Part B IV RC-P Dose Cohorts



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5.2. Study Treatment

Dosages (mg/m^2) will be administered based on the patient's body surface area (BSA), and calculated using the patient's height and weight taken prior to the start of each course. Patients will receive doses of either RC-P via the IM or IV route depending on whether they are enrolled in Part A (IM) or Part B (IV) of the study. All other chemotherapy will continue according to the therapeutic regimen as defined in the patient's original treatment protocol for the patient's ALL/LBL.

In Part A of the study, RC-P will be administered via the IM route. For IM RC-P Dose Cohort 1, the starting dose of RC-P will be 25 mg/m^2 with 6 IM RC-P doses.

In Part B of the study, RC-P will be administered via the IV route. For IV RC-P Dose Cohort 1, the starting dose of RC-P is planned to be 37.5 mg/m^2 with 6 IV RC-P doses.

5.3. Power and Sample Size Considerations

For Part A of the study, 98 patients administered the final IM dose level are planned.

For the final IM RC-P dose level, 13 evaluable patients are planned in Part A Cohort 1 (IM RC-P Dose Confirmation), and approximately 85 patients are planned in Cohort 2 (IM Expansion) to obtain 98 patients in total at the final dose in Part A for the primary efficacy analysis of the IM administration route.

The sample size of 13 evaluable patients in Part A Cohort 1 provides at least 80% posterior probability of the true response rate $\geq$ 96% given 100% response rate in Cohort 1 and non-informative neutral beta prior with $\alpha = \beta = 1/3$.

Since the primary efficacy endpoint is considered to be met if the lower bound of the 95% Wald confidence interval (CI) of the response rate exceeds 90%, the final sample size is planned as 98 patients which provides 83% probability that the lower bound of the 95% Wald CI exceeds 90%, assuming a true response rate of 96% for the primary efficacy endpoint and a 5% drop out rate. Furthermore, with a sample size of 98 patients, the probability of observing at least one adverse events (AE) related to asparaginase with an incidence as low as 3% is 95%.

For the primary efficacy assessment at the primary analysis, a minimum of 93 patients in the Efficacy Analysis Set are required. This means at least 93 patients received at least one dose of the final IM RC-P dose level, and had at least one 72-hour NSAA assessment collected within the protocol-defined sample collection window (± 2 hours) in Course 1. If fewer than 93 out of 98 patients have the necessary data, additional patients will be enrolled to ensure 93 patients for analysis.

One interim analysis with 51 patients is planned. At the interim analysis, a sample size of 51 patients provides 70% probability that the lower bound of the 95% CI exceeds 90% under the assumption of a 96% true response rate and a 5% drop out rate. The probability of observing at least one AE related to asparaginase with an incidence as low as 3% is 79% with 51 patients.

Similar to the primary analysis, a minimum of 48 patients in the Efficacy Analysis Set for the primary efficacy assessment are necessary for the interim analysis. If fewer than 48 out of 51 patients have the necessary data, additional patients will be enrolled to ensure 48 patients for analysis.

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For Part B, a target of at least 6 evaluable patients will be administered the first IV dose level. This sample size is not based on formal power calculation but provides an initial assessment of the IV RC-P dosing.

5.4. Randomization and Blinding

This is an open-label study; there will be no blinding. Participants to the study will not be randomized.

5.5. Interim Analysis

This study has one interim analysis planned after the 51st patient completes Course 1 with the final IM RC-P dose level (Cohort 1 and Cohort 2 patients). If the primary endpoint is met at the interim analysis, the enrollment to this cohort will be stopped early for efficacy. If the incidence of allergic reactions (including hypersensitivity and anaphylaxis) related to RC-P exceeds 25%, or the incidence of pancreatitis exceeds 10% or thrombosis exceeds 10% at this interim analysis, enrollment into this Expansion Cohort may be stopped for safety.

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6. ANALYSIS SETS

For purposes of analysis, the following populations are defined.

Analysis Set	Description
Enrolled Analysis Set	The Enrolled Analysis Set includes patients who signed the informed consent and meet inclusion/exclusion criteria per investigator.
Efficacy Analysis Set	The Efficacy Analysis Set includes patients who received at least one dose of RC-P and had at least one 48- or 72-hour NSAA assessment collected within the protocol defined sample collection window (± 2 hours) in Course 1. This will be the primary analysis set for the primary efficacy endpoint and all other efficacy endpoints.
Safety Analysis Set	The Safety Analysis Set will include patients who received at least one dose of RC-P. This will be the primary analysis set for the primary safety endpoint and all other safety endpoints.
PK Analysis Set	The PK Analysis Set will include patients who received at least one dose of RC-P and have at least one post-dose evaluable SAA or PK concentration value. This will be used for all descriptive PK summaries.
PD Analysis Set	The Pharmacodynamics (PD) Analysis Set will include patients who received at least one dose of RC-P and have at least one post-dose evaluable L-asparagine or L-glutamine value. This will be used for all descriptive PD summaries.

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7. GENERAL ASPECTS FOR STATISTICAL ANALYSIS

The statistical principles applied in the design and planned analyses of this study are consistent with International Conference for Harmonisation (ICH) E9 guidelines (ICH 1998).

7.1. General Methods

Unless otherwise specified, continuous data will be summarized using descriptive statistics comprising of the number of patients with data to be summarized (n), mean, standard deviation (SD), median, minimum (min) and maximum (max), by time, dose level of RC-P, and route of administration (IM or IV) as appropriate. Categorical variables will be presented using counts and percentages.

Unless otherwise specified, analyses and summary outputs will be generated using SAS® version 9.*4* (or higher).

7.2. Study Day 1 and Baseline Value Definitions

7.2.1. Study Day 1

Study Day 1 is defined as the date of the first dose of RC-P.

7.2.2. Baseline Value

A baseline value is defined as the latest non-missing value obtained prior to or at the start date and/or time of the first dose of RC-P.

7.2.3. Study Day

Study Day is calculated relative to Study Day 1 as follows:

- If the date of the event is on or after Study Day 1,

  Study Day = (date of event - Study Day 1) +1.
- If the date of the event is prior to Study Day 1,

  Study Day = (date of event - Study Day 1).

7.2.4. Visit Windows

Not applicable.

7.2.5. Missing and Partial Data

Any missing AE information such as severity and relationship will be handled as described in Section 10.2 and Appendix I.

Missing PK levels will be handled as described in Section 11.

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7.3. Hypotheses Testing, Level of Significance and Multiplicity Adjustment

No formal statistical testing is planned for this study and thus no multiplicity adjustment is applicable.

7.4. Subgroups and Subgroup Analyses

Exploratory analyses of the primary efficacy, secondary efficacy, and safety endpoints may be conducted for the following subgroups of interest:

- Pediatric (<18) *vs* adult (≥ 18)
- Patients with prior allergic reaction to an *E. coli*-derived asparaginase *vs* silent inactivation
- Patients with Grade 2 allergic reaction *vs* Grade 3 allergic reactions

7.5. Changes to Planned Analyses

Sensitivity analyses were added to assess COVID-19 impact on the primary (Section 9.1.3) and key secondary (Section 9.2.3) efficacy endpoint. Additional subgroup analyses for the primary (Section 9.1.4) and secondary (Section 9.2.4) efficacy endpoints which are not specified in the protocol may be performed.

Summary of protocol deviations due to COVID-19 was newly added in Section 13.

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8. STUDY POPULATION SUMMARIES

8.1. Enrollment

Listings of inclusion/exclusion criteria for enrollment will be provided.

8.2. Subject Disposition

The summary of patient disposition will include the number of patients screened, screen failure patients who were not enrolled with summary of reasons, patients in the Enrolled Analysis Set, and patients in the following categories:

Study Drug Completion

- Received at least one dose of study drug treatment
- Ongoing study drug treatment
- Completed study drug treatment
- Discontinued study drug treatment with summary of reasons for discontinuing study drug treatment

Study Completion

- Ongoing study
- Completed study
- Discontinued study with summary of reasons for discontinuing study

This summary will be provided by dose level of RC-P and route of administration (IM or IV).

A separate summary of the study analysis sets will be provided to include the number of patients in the Enrolled Analysis Set, patients in the Efficacy Analysis Set, patients in the Safety Analysis set, patients in the PK Analysis Set, and patients in PD Analysis Set.

A listing of patient disposition with study analysis set, study drug completion and study completion status will be provided.

8.3. Demographic and Baseline Characteristics

Patient demographics (e.g. gender, race, ethnicity, and age at enrollment) and baseline characteristics (e.g. weight, height, body mass index [BMI], and BSA) will be summarized by dose level of RC-P and route of administration (IM or IV) for the Efficacy, Safety, and PK Analysis Sets. A listing of demographic and baseline characteristics will be provided for Safety Analysis Set.

In addition, the following baseline characteristics and medical history will be summarized:

- Primary disease (ALL vs LBL)
- Time since primary disease diagnosis to Study Day 1
- Prior asparaginase treatment
- Time since last asparaginase received to Study Day 1

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- Prior Grade 2 *vs* Grade 3 allergic reaction to an *E. coli*-derived asparaginase *vs* silent inactivation

No formal statistical comparisons will be performed.

8.4. Medical History

Medical history will be coded using the MedDRA 22.1 and listed by dose level of RC-P, route of administration (IM or IV), system organ class (SOC), and preferred term (PT) for Safety Analysis Set. For data presentation, SOC will be ordered alphabetically, with PT sorted by decreasing frequency in the final dose of IM.

8.5. Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary and will be summarized separately by dose level of RC-P and route of administration (IM or IV) for the Safety Analysis Set.

Prior medications are defined as those medications taken prior to Study Day 1. Concomitant medications are defined as medications taken at any time on or after Study Day 1. If any medications were taken prior to Study Day 1 and continued to or after Study Day 1, it will be counted as both prior and concomitant medications. Like AEs, prior and concomitant definitions for medications will be derived after taking into consideration any partial or completely missing start and end dates (See Appendix I).

Listings of prior medications and concomitant medications will be provided separately.

8.6. Protocol Deviations

Major protocol deviations will be summarized by dose level of RC-P and route of administration (IM or IV) using the Safety Analysis Set. All protocol deviations will be listed.

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9. EFFICACY

9.1. Primary Efficacy Endpoint and Analysis

9.1.1. Primary Efficacy Endpoint

The primary efficacy endpoint of the study is the response rate, defined as the proportion of patients with the last 72-hour NSAA level ≥ 0.1 IU/mL during the first course of IM administration of RC-P. Patients in both Part A Cohort 1 and Cohort 2 at the final IM RC-P dose level will be included. Depending on the RC-P start day for a patient, this could be predose 4 if the first course of RC-P started on a Monday; predose 6 if the first course of RC-P started on a Wednesday; or predose 5 if the first course of RC-P started on a Friday.

9.1.2. Analysis of the Primary Efficacy Endpoint

The primary efficacy endpoint will be estimated using the Efficacy Analysis Set for patients administered the final IM RC-P dose level with at least one 72-hour NSAA assessment collected within the protocol defined sample collection window (± 2 hours) in Course 1 of Part A. The last observed 72-hour NSAA assessment collected within the protocol defined sample collection window (± 2 hours) in Course 1 will be used in the calculation of the primary efficacy endpoint. Missing data will not be imputed. The response rate, along with the 95% Wald CI will be provided. The primary efficacy endpoint will be met if the lower bound of the 95% CI of the response rate exceeds 90%.

9.1.3. Sensitivity Analyses

A sensitivity analysis will be performed to assess COVID-19 impact on the primary efficacy endpoint. Patients in the Efficacy Analysis Set who missed any PK sample collections in Course 1 due to COVID-19 will be excluded from the analysis. The response rate for this subset along with the 95% Wald CI will be provided.

9.1.4. Subgroup Analyses

The primary efficacy endpoint will be analyzed for the patient subgroups specified in Section 7.4.

9.2. Secondary Efficacy Endpoints and Analyses

9.2.1. Key Secondary Efficacy Endpoint

The key secondary efficacy endpoint of the study is the response rate, defined as the proportion of patients with the last 48-hour NSAA level ≥ 0.1 IU/mL during the first course of IM administration of RC-P.

The key secondary efficacy endpoint will be analyzed using the Efficacy Analysis Set for patients administered the final IM RC-P dose level with at least one 48-hour NSAA assessment collected within the protocol defined sample collection window (± 2 hours) in Course 1 of Part A. The last observed 48-hour NSAA assessment collected within the protocol defined sample collection window (± 2 hours) in Course 1 will be used in the calculation of the key secondary efficacy endpoint. Missing data will not be imputed. The response rate, along with the 95% Wald CI will

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be provided. The key secondary efficacy endpoint will be met if the lower bound of the 95% CI of the response rate exceeds 90%.

9.2.2. Other Secondary Efficacy Endpoints

Other secondary efficacy endpoints in Part A include the following:

- Proportion of patients with the last 48-hour NSAA level ≥ 0.4 IU/mL during the first course of IM administration of RC-P
- Proportion of patients with the last 72-hour NSAA level ≥ 0.4 IU/mL during the first course of IM administration of RC-P

9.2.2.1. Proportion of Patients with the Last 48-hour NSAA Level ≥ 0.4 IU/mL during the First Course of IM Administration of RC-P

The proportion of patients with the last 48-hour NSAA level ≥ 0.4 IU/mL during the first course of IM administration of RC-P will be analyzed using the Efficacy Analysis Set for patients administered the final IM RC-P dose level with at least one 48-hour NSAA assessment collected within the protocol defined sample collection window (± 2 hours) in Course 1 of Part A. The last observed 48-hour NSAA assessment collected within the protocol defined sample collection window (± 2 hours) in Course 1 will be used in the calculation of this endpoint. Missing data will not be imputed. The response rate, along with the 95% Wald CI will be provided.

9.2.2.2. Proportion of Patients with the Last 72-hour NSAA Level ≥ 0.4 IU/mL during the First Course of IM Administration of RC-P

The proportion of patients with the last 72-hour NSAA level ≥ 0.4 IU/mL during the first course of IM administration of RC-P will be analyzed using the Efficacy Analysis Set for patients administered the final IM RC-P dose level with at least one 72-hour NSAA assessment collected within the protocol defined sample collection window (± 2 hours) in Course 1 of Part A. The last observed 72-hour NSAA assessment collected within the protocol defined sample collection window (± 2 hours) in Course 1 will be used in the calculation of this endpoint. Missing data will not be imputed. The response rate, along with the 95% Wald CI will be provided.

9.2.3. Sensitivity analyses

A sensitivity analysis will be performed to assess COVID-19 impact on the key secondary efficacy endpoint. Patients in the Efficacy Analysis Set who missed any PK sample collections in Course 1 due to COVID-19 will be excluded from the analysis. The response rate for this subset along with the 95% Wald CI will be provided.

9.2.4. Subgroup Analyses

The key and other secondary efficacy endpoints will be analyzed for the patient subgroups specified in Section 7.4.

9.3. Exploratory Efficacy Endpoints and Analyses

Exploratory efficacy endpoints include the following from Part B of the study:

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- Proportion of patients with the last 48-hour NSAA level ≥ 0.1 IU/mL during the first course of IV administration of RC-P
- Proportion of patients with the last 72-hour NSAA level ≥ 0.1 IU/mL during the first course of IV administration of RC-P
- Proportion of patients with the last 48-hour NSAA levels ≥ 0.4 IU/mL during the first course of IV administration of RC-P
- Proportion of patients with the last 72-hour NSAA level ≥ 0.4 IU/mL during the first course of IV administration of RC-P

9.3.1. Proportion of patients with the Last 48-hour NSAA level ≥ 0.1 IU/mL during the first course of IV administration of RC-P

The proportion of patients with the last 48-hour NSAA level ≥ 0.1 IU/mL during the first course of IV administration of RC-P will be analyzed using the Efficacy Analysis Set for patients administered the final IV RC-P dose level with at least one 48-hour NSAA assessment collected within the protocol defined sample collection window (± 2 hours) in Course 1 of Part B. The last observed 48-hour NSAA assessment collected within the protocol defined sample collection window (± 2 hours) in Course 1 will be used in the calculation of this endpoint. Missing data will not be imputed. The response rate, along with the 95% CI will be provided.

9.3.2. Proportion of patients with the Last 72-hour NSAA level ≥ 0.1 IU/mL during the first course of IV administration of RC-P

The proportion of patients with the last 72-hour NSAA level ≥ 0.1 IU/mL during the first course of IV administration of RC-P will be analyzed using the Efficacy Analysis Set for patients administered the final IV RC-P dose level with at least one 72-hour NSAA assessment collected within the protocol defined sample collection window (± 2 hours) in Course 1 of Part B. The last observed 72-hour NSAA assessment collected within the protocol defined sample collection window (± 2 hours) in Course 1 will be used in the calculation of this endpoint. Missing data will not be imputed. The response rate, along with the 95% CI will be provided.

9.3.3. Proportion of patients with the Last 48-hour NSAA level ≥ 0.4 IU/mL during the first course of IV administration of RC-P

The proportion of patients with the last 48-hour NSAA level ≥ 0.4 IU/mL during the first course of IV administration of RC-P will be analyzed using the Efficacy Analysis Set for patients administered the final IV RC-P dose level with at least one 48-hour NSAA assessment collected within the protocol defined sample collection window (± 2 hours) in Course 1 of Part B. The last observed 48-hour NSAA assessment collected within the protocol defined sample collection window (± 2 hours) in Course 1 will be used in the calculation of this endpoint. Missing data will not be imputed. The response rate, along with the 95% CI will be provided.

9.3.4. Proportion of patients with the Last 72-hour NSAA level ≥ 0.4 IU/mL during the first course of IV administration of RC-P

The proportion of patients with the last 72-hour NSAA level ≥ 0.4 IU/mL during the first course of IV administration of RC-P will be analyzed using the Efficacy Analysis Set for patients

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administered the final IV RC-P dose level with at least one 72-hour NSAA assessment collected within the protocol defined sample collection window (± 2 hours) in Course 1 of Part B. The last observed 72-hour NSAA assessment collected within the protocol defined sample collection window (± 2 hours) in Course 1 will be used in the calculation of this endpoint. Missing data will not be imputed. The response rate, along with the 95% CI will be provided.

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10. SAFETY

Safety analyses will be summarized by dose level of RC-P, and route of administration (IM or IV) using the Safety Analysis Set. No formal statistical testing will be performed for the safety analyses.

10.1. Exposure

10.1.1. Extent of Exposure

The summary of *i*) planned and actual RC-P administration status by course, and *ii*) the descriptive summary of planned and actual number of courses of RC-P will be provided. Study drug administration details such as the course number, actual dose, start and end day/time of the study drug administration will be listed separately.

10.1.2. Treatment Compliance

Not applicable for this study since RC-P administration will vary depending on the number of doses of a long-acting *E. coli*-derived asparaginase remaining on an individual patient's original treatment protocol.

10.2. Adverse Events

AEs recorded in the case report form will be coded to system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA 22.1). The investigator will assess the relatedness of each AE to study drug. The severity of AEs will be recorded using the Common Terminology Criteria for Adverse Events (CTCAE 5.0).

At a minimum, the investigator must record all AEs that occur from the time written informed consent is obtained until screen failure if applicable, or 30 days after the patient's last dose of the last course of RC-P, regardless of their relationship to study drug. Any serious AE (SAE) assessed as related to study drug by the investigator that occurs more than 30 days after the patient's last dose of the last course of RC-P should be reported regardless of time after study termination.

A treatment-emergent adverse event (TEAE) is defined as any event with onset date on or after Study Day 1 through the end of the study or any ongoing event that worsens in severity after Study Day 1 through the end of the study. Only TEAEs with the onset date through the end of the AE reporting period will be included in summary tables unless otherwise specified. For the purpose of calculating treatment emergence, incomplete onset dates will be imputed as detailed in Appendix I.

AEs are graded by the investigator as Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe or medically significant but not immediately life-threatening), Grade 4 (life-threatening consequences), or Grade 5 (Death related to AE). The severity grade of events for which the investigator did not record severity will be categorized as "missing" for tabular summaries and data listings, and will be considered the least severe for the purposes of sorting for data presentation.

Treatment-related AEs are those for which the investigator answers "Yes" to the question "Was this adverse event related to study treatment?" in the eCRF. Events for which the investigator did not record relationship to study treatment will be considered related to study treatment for summary purpose. Data listings will show treatment-relationship as missing. AEs for which "Yes"

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is marked for question "Was this adverse event related to study procedure?" in eCRF will be identified and included in AE listing.

SAEs are those for which the investigator answers "Yes" to the question "Was the adverse event serious?" in the eCRF. The clinical database will be reconciled with the SAE database before database finalization.

For all AE summaries, if a patient has more than 1 AE within a PT, the patient is counted only once at the maximum severity and with the closest relationship to study drug. If a patient has more than 1 AE within a SOC, the patient is similarly counted once when reporting results for that SOC.

A brief summary of TEAEs (i.e., the number and percentage of patients) will be presented by dose level of RC-P, and route of administration (IM or IV) for the following: (1) any TEAE, (2) any serious TEAE, (3) any treatment-related TEAE, (4) any serious treatment-related TEAE, (5) any Grade 3 or 4 TEAE, (6) any treatment-related Grade 3 or 4 TEAE, (7) any TEAE leading to study drug discontinuation, (8) any treatment-related TEAE leading to study drug discontinuation, (9) any TEAE leading to death, and (10) any treatment-related TEAE leading to death.

A general summary of TEAEs by SOC and PT will be provided with the number and percent of patients who experienced the following types of events by dose level of RC-P, and route of administration (IM or IV). For data presentation, SOC will be ordered alphabetically, with PT sorted by decreasing frequency in the final dose of IM:

- Patients with any TEAE
- Patients with any serious TEAE
- Patients with any treatment-related TEAE
- Patients with any serious treatment-related TEAE
- Patients with any Grade 3 or 4 TEAE
- Patients with any treatment-related Grade 3 or 4 TEAE
- Patients with any TEAE leading to study drug discontinuation
- Patients with any treatment-related TEAE leading to study drug discontinuation
- Patients with any TEAE leading to death
- Patients with any treatment-related TEAE leading to death

Data listings will be provided for the following including patient number, dose level of RC-P, route of administration (IM or IV), SOC, PT, date of onset/stop, severity, seriousness, treatment-relationship, action taken:

- All AEs
- Serious AEs
- Treatment-related AEs
- Serious treatment-related AEs
- Grade 3 and 4 AEs

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- AEs leading to study drug discontinuation
- Death report

10.2.1. Adverse Events of Special Interest

AEs of special interest - allergic reactions (including hypersensitivity and anaphylaxis), pancreatitis, and thrombosis - will be summarized by dose level of RC-P, route of administration (IM or IV), and patients subgroups specified in Section 7.4. The list of PTs used to search each AEs of special interest, reviewed by Jazz Drug Safety & Pharmacovigilance, is provided in Appendix II.

10.3. Laboratory Assessments

Baseline value, post-baseline value, and changes from baseline value for all hematology, coagulation, and chemistry parameters will be summarized by dose level of RC-P and route of administration (IM or IV) using descriptive statistics.

10.4. Vital Signs

Baseline value, post-baseline value, and changes from baseline value for all vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate) and body temperature will be summarized by dose level of RC-P and route of administration (IM or IV) using descriptive statistics.

10.5. Other Safety Endpoints

A data listing will be provided for patients experiencing pregnancy during the study.

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11. PHARMACOKINETIC/PHARMACODYNAMIC ANALYSES

The summary and listings of RC-P PK (SAA and serum asparaginase concentration levels) and PD (asparagine and glutamine concentrations) measurements will be provided. Descriptive statistics including number of patients, mean, SD, median, min, max, coefficient of variation (CV), geometric mean, and geometric standard deviation will be used to summarize PK and PD data by time, dose level, Course, and route of administration (IM or IV), as appropriate. Proportion of patients with NSAA ≥ 0.1 and ≥ 0.4 IU/mL by time will also be summarized for SAA data.

Individual and/or summary figures of SAA-time or enzyme concentration-time profiles in serum may be provided. Individual and/or summary figures of SAA versus PD profiles may also be provided.

Statistical summaries and displays will be based on scheduled sampling times unless significant deviations occur (outside of the specified time windows in Appendix 2 in protocol). Differences between scheduled and actual sampling times will be listed for all patients.

RC-P SAA data will be used in a population PK analysis. A population PK model will be used to characterize the RC-P PK profiles in patients with ALL/LBL following hypersensitivity to *E. coli*-derived asparaginases, and to explore exposure-response correlations. Results from the population PK analysis will be reported separately from the CSR, in a standalone document.

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12. IMMUNOGENICITY

The summary of immunogenicity results will be provided by dose level, Course, and route of administration (IM or IV) as appropriate. Immunogenicity results will be also listed as positive or negative for the presence of ADA for each patient by dose level, Course, and route of administration (IM or IV), as appropriate. In addition, for all ADA positive samples, titer values will be provided as a quantification measurement of antibodies.

For those with positive ADA results, individual profile may be provided to present ADA and hypersensitivity onset time along with each course start time. Boxplots of serum asparaginase activity levels by ADA status may also be provided.

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13. COVID-19

Data identifying missed visits, missed assessments, study drug discontinuation, and/or study participation termination due to COVID-19 will be captured either in EDC (study drug discontinuation and study participation termination) or protocol deviation log (missed visits and missed assessments). The collected data will specify if the study disruption was due to acquiring COVID-19 or due to other COVID-19 restrictions.

A summary of major protocol deviations due to COVID-19 will be provided. A listing of all disruptions due to COVID-19 will be provided (i.e. missed visits, missed assessments, study drug discontinuation, and study participation termination).

REFERENCES

Not applicable.

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APPENDIX I. DATE IMPUTATION RULES

Incomplete Adverse Event Onset Date

If *year* is missing (or completely missing): set to the date of first dose.

If (*year* is present and *month* and *day* are missing) or (*year* and *day* are present and *month* is missing):

If *year* = year of first dose: set the date to the first dose date.

If *year* < year of first dose: set *month* and *day* to December 31st.

If *year* > year of first dose: set *month* and *day* to January 1st.

If *month* and *year* are present and *day* is missing:

If *year* = year of first dose, and:

If *month* = month of first dose: set *day* to day of first dose.

If *month* < month of first dose: set *day* to last day of *month*.

If *month* > month of first dose: set *day* to 1st day of *month*.

If *year* < year of first dose: set *day* to last day of month.

If *year* > year of first dose: set *day* to 1st day of month.

For all other cases: set to date of first dose.

Incomplete Concomitant Medication Start Date

If *year* is missing (or completely missing): do not impute.

If (*year* is present and *month* and *day* are missing) or (*year* and *day* are present and *month* is missing):

Set *month* and day to January 1st.

If *year* and *month* are present and *day* is missing:

Set *day* to 1st day of month.

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Incomplete Concomitant Medication End Date

Do not impute if Ongoing Flag is checked.

If *year* is missing (or completely missing): do not impute.

If (*year* is present and *month* and *day* are missing) or (*year* and *day* are present and *month* is missing):

Set *month* and day to December 31st.

If *year* and *month* are present and *day* is missing:

Set *day* to last day of the month.

Incomplete Subsequent Anti-Leukemic/Cancer Therapy Start Date

Assumption: Anti-Cancer therapies reported on the Subsequent Anti-Leukemic/Cancer Therapy eCRF.

If *year* is missing (or completely missing): set to date of last dose of study treatment + 1

If (*year* is present and *month* and *day* are missing) or (*year* and *day* are present and *month* is missing):

If *year* > year of the last dose: Set *month* and *day* to January 1st.

If *year* = year of the last dose: Set *month* and *day* to date of last dose of study treatment + 1

If *year* and *month* are present and *day* is missing:

Set *day* to 1st day of month if the resulting imputed date is greater than date of last dose. Otherwise set the imputed date to date of last dose + 1

NOTE: If progressive disease/Relapse date is available and after date of last dose, replace last dose of study drug with progressive disease/Relapse date for imputation algorithm given in this section.

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APPENDIX II. PTS USED TO SEARCH AES OF SPECIAL INTEREST

List of PTs under the narrow SMQs for Hypersensitivity

Acquired C1 inhibitor deficiency
Acute generalised exanthematous pustulosis
Administration related reaction
Administration site dermatitis
Administration site eczema
Administration site hypersensitivity
Administration site rash
Administration site recall reaction
Administration site urticaria
Administration site vasculitis
Allergic bronchitis
Allergic colitis
Allergic cough
Allergic cystitis
Allergic eosinophilia
Allergic gastroenteritis
Allergic hepatitis
Allergic keratitis
Allergic oedema
Allergic otitis externa
Allergic otitis media
Allergic pharyngitis
Allergic reaction to excipient
Allergic respiratory disease
Allergic respiratory symptom
Allergic sinusitis
Allergic stomatitis
Allergic transfusion reaction
Allergy alert test positive
Allergy test positive
Allergy to immunoglobulin therapy
Allergy to surgical sutures
Allergy to vaccine
Anal eczema
Anaphylactic reaction
Anaphylactic shock
Anaphylactic transfusion reaction

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Anaphylactoid reaction
Anaphylactoid shock
Anaphylaxis treatment
Angioedema
Antiallergic therapy
Antiendomysial antibody positive
Anti-neutrophil cytoplasmic antibody positive vasculitis
Application site dermatitis
Application site eczema
Application site hypersensitivity
Application site rash
Application site recall reaction
Application site urticaria
Application site vasculitis
Arthritis allergic
Aspirin-exacerbated respiratory disease
Atopic cough
Atopy
Blepharitis allergic
Blood immunoglobulin E abnormal
Blood immunoglobulin E increased
Bromoderma
Bronchospasm
Catheter site dermatitis
Catheter site eczema
Catheter site hypersensitivity
Catheter site rash
Catheter site urticaria
Catheter site vasculitis
Chronic eosinophilic rhinosinusitis
Chronic hyperplastic eosinophilic sinusitis
Circulatory collapse
Circumoral oedema
Circumoral swelling
Conjunctival oedema
Conjunctivitis allergic
Contact stomatitis
Contrast media allergy
Contrast media reaction
Corneal oedema
Cutaneous vasculitis

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Dennie-Morgan fold
Dermatitis
Dermatitis acneiform
Dermatitis allergic
Dermatitis atopic
Dermatitis bullous
Dermatitis contact
Dermatitis exfoliative
Dermatitis exfoliative generalised
Dermatitis herpetiformis
Dermatitis infected
Dermatitis psoriasiform
Device allergy
Dialysis membrane reaction
Distributive shock
Documented hypersensitivity to administered product
Drug eruption
Drug hypersensitivity
Drug provocation test
Drug reaction with eosinophilia and systemic symptoms
Eczema
Eczema infantile
Eczema nummular
Eczema vaccinatum
Eczema vesicular
Eczema weeping
Encephalitis allergic
Encephalopathy allergic
Eosinophilic granulomatosis with polyangiitis
Epidermal necrosis
Epidermolysis
Epidermolysis bullosa
Epiglottic oedema
Erythema multiforme
Erythema nodosum
Exfoliative rash
Eye allergy
Eye oedema
Eye swelling
Eyelid oedema
Face oedema

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Fixed eruption
Giant papillary conjunctivitis
Gingival oedema
Gingival swelling
Gleich's syndrome
Haemorrhagic urticaria
Hand dermatitis
Henoch-Schonlein purpura
Henoch-Schonlein purpura nephritis
Heparin-induced thrombocytopenia
Hereditary angioedema
Hereditary angioedema with C1 esterase inhibitor deficiency
Hypersensitivity
Hypersensitivity myocarditis
Hypersensitivity pneumonitis
Hypersensitivity vasculitis
Idiopathic urticaria
Immediate post-injection reaction
Immune thrombocytopenic purpura
Immune tolerance induction
Implant site dermatitis
Implant site hypersensitivity
Implant site rash
Implant site urticaria
Incision site dermatitis
Incision site rash
Infusion related hypersensitivity reaction
Infusion related reaction
Infusion site dermatitis
Infusion site eczema
Infusion site hypersensitivity
Infusion site rash
Infusion site recall reaction
Infusion site urticaria
Infusion site vasculitis
Injection related reaction
Injection site dermatitis
Injection site eczema
Injection site hypersensitivity
Injection site rash
Injection site recall reaction

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Injection site urticaria
Injection site vasculitis
Instillation site hypersensitivity
Instillation site rash
Instillation site urticaria
Interstitial granulomatous dermatitis
Intestinal angioedema
Iodine allergy
Kaposi's varicelliform eruption
Kounis syndrome
Laryngeal oedema
Laryngitis allergic
Laryngospasm
Laryngotracheal oedema
Limbal swelling
Lip oedema
Lip swelling
Mast cell degranulation present
Medical device site dermatitis
Medical device site eczema
Medical device site hypersensitivity
Medical device site rash
Medical device site recall reaction
Medical device site urticaria
Mouth swelling
Mucocutaneous rash
Multiple allergies
Nephritis allergic
Nikolsky's sign
Nodular rash
Oculomucocutaneous syndrome
Oculorespiratory syndrome
Oedema mouth
Oral allergy syndrome
Oropharyngeal blistering
Oropharyngeal oedema
Oropharyngeal spasm
Oropharyngeal swelling
Palatal oedema
Palatal swelling
Palisaded neutrophilic granulomatous dermatitis

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Palpable purpura
Pathergy reaction
Perioral dermatitis
Periorbital oedema
Periorbital swelling
Pharyngeal oedema
Pharyngeal swelling
Procedural shock
Pruritus allergic
Radioallergosorbent test positive
Rash
Rash erythematous
Rash follicular
Rash macular
Rash maculo-papular
Rash maculovesicular
Rash morbilliform
Rash neonatal
Rash papulosquamous
Rash pruritic
Rash pustular
Rash rubelliform
Rash scarlatiniform
Rash vesicular
Reaction to azo-dyes
Reaction to colouring
Reaction to excipient
Reaction to food additive
Reaction to preservatives
Red man syndrome
Rhinitis allergic
Scleral oedema
Scleritis allergic
Scrotal eczema
Scrotal oedema
Serum sickness
Serum sickness-like reaction
Shock
Shock symptom
SJS-TEN overlap
Skin necrosis

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Skin reaction
Skin test positive
Solar urticaria
Solvent sensitivity
Stevens-Johnson syndrome
Stoma site hypersensitivity
Stoma site rash
Swelling face
Swelling of eyelid
Swollen tongue
Symmetrical drug-related intertriginous and flexural exanthema
Therapeutic product cross-reactivity
Tongue oedema
Toxic epidermal necrolysis
Toxic skin eruption
Tracheal oedema
Type I hypersensitivity
Type II hypersensitivity
Type III immune complex mediated reaction
Type IV hypersensitivity reaction
Urticaria
Urticaria cholinergic
Urticaria chronic
Urticaria contact
Urticaria papular
Urticaria physical
Urticaria pigmentosa
Urticaria vesiculosa
Urticarial dermatitis
Urticarial vasculitis
Vaccination site dermatitis
Vaccination site eczema
Vaccination site exfoliation
Vaccination site hypersensitivity
Vaccination site rash
Vaccination site recall reaction
Vaccination site urticaria
Vaccination site vasculitis
Vaccination site vesicles
Vaginal exfoliation
Vaginal ulceration

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Vasculitic rash
Vernal keratoconjunctivitis
Vessel puncture site rash
Vessel puncture site vesicles
Vulval eczema
Vulval ulceration
Vulvovaginal rash
Vulvovaginal ulceration
Vulvovaginitis allergic

List of PTs under the narrow SMQs for Anaphylactic Reaction

Anaphylactic reaction
Anaphylactic shock
Anaphylactic transfusion reaction
Anaphylactoid reaction
Anaphylactoid shock
Circulatory collapse
Dialysis membrane reaction
Kounis syndrome
Procedural shock
Shock
Shock symptom
Type I hypersensitivity

List of PTs for Pancreatitis

Alcoholic pancreatitis
Autoimmune pancreatitis
Cytomegalovirus pancreatitis
Haemorrhagic necrotic pancreatitis
Hereditary pancreatitis
Immune-mediated pancreatitis
Ischaemic pancreatitis
Lupus pancreatitis
Obstructive pancreatitis
Oedematous pancreatitis
Pancreatitis
Pancreatitis acute
Pancreatitis bacterial
Pancreatitis chronic
Pancreatitis fungal
Pancreatitis haemorrhagic
Pancreatitis helminthic
Pancreatitis mumps

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Pancreatitis necrotising
Pancreatitis relapsing
Pancreatitis viral
Radiation pancreatitis
Traumatic pancreatitis

List of PTs for Thrombosis

Administration site thrombosis
Adrenal thrombosis
Aortic thrombosis
Application site thrombosis
Arterial bypass thrombosis
Arterial thrombosis
Arteriovenous fistula thrombosis
Arteriovenous graft thrombosis
Atrial thrombosis
Axillary vein thrombosis
Basilar artery thrombosis
Brachiocephalic vein thrombosis
Brain stem thrombosis
Cardiac ventricular thrombosis
Carotid artery thrombosis
Catheter site thrombosis
Cavernous sinus thrombosis
Cerebellar artery thrombosis
Cerebral artery thrombosis
Cerebral thrombosis
Cerebral venous sinus thrombosis
Cerebral venous thrombosis
Coronary artery thrombosis
Coronary bypass thrombosis
Deep vein thrombosis
Deep vein thrombosis postoperative
Device related thrombosis
Foetal placental thrombosis
Graft thrombosis
Hepatic artery thrombosis
Hepatic vascular thrombosis
Hepatic vein thrombosis
Implant site thrombosis
Infective thrombosis
Infusion site thrombosis
Injection site thrombosis
Instillation site thrombosis
Intrapericardial thrombosis
Jugular vein thrombosis

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Medical device site thrombosis
Mesenteric artery thrombosis
Mesenteric vein thrombosis
Ophthalmic artery thrombosis
Ophthalmic vein thrombosis
Ovarian vein thrombosis
Paraneoplastic thrombosis
Pelvic venous thrombosis
Penile vein thrombosis
Peripheral artery thrombosis
Portal vein thrombosis
Portosplenomesenteric venous thrombosis
Postoperative thrombosis
Postpartum thrombosis
Postpartum venous thrombosis
Precerebral artery thrombosis
Prosthetic cardiac valve thrombosis
Pulmonary artery thrombosis
Pulmonary embolism
Pulmonary thrombosis
Pulmonary venous thrombosis
Renal artery thrombosis
Renal vascular thrombosis
Renal vein thrombosis
Retinal artery thrombosis
Retinal vascular thrombosis
Retinal vein thrombosis
Shunt thrombosis
Spinal artery thrombosis
Splenic artery thrombosis
Splenic thrombosis
Splenic vein thrombosis
Stoma site thrombosis
Subclavian artery thrombosis
Subclavian vein thrombosis
Superior sagittal sinus thrombosis
Thrombosis
Thrombosis corpora cavernosa
Thrombosis in device
Thrombosis mesenteric vessel
Thrombosis prophylaxis
Transverse sinus thrombosis
Truncus coeliacus thrombosis
Tumour thrombosis
Umbilical cord thrombosis
Vaccination site thrombosis

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Vascular access site thrombosis
Vascular graft thrombosis
Vascular pseudoaneurysm thrombosis
Vascular stent thrombosis
Vena cava thrombosis
Venous thrombosis
Venous thrombosis in pregnancy
Venous thrombosis limb
Venous thrombosis neonatal
Vertebral artery thrombosis
Vessel puncture site thrombosis
Visceral venous thrombosis