CLINICAL STUDY PROTOCOL: JZP458-201

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
Study Phase:	Pivotal Phase 2/3
Product Name:	Recombinant Crisantaspase *Pseudomonas fluorescens* (RC-P), JZP-458
IND Number:	IND 129622
Indication:	Acute Lymphoblastic Leukemia (ALL)/Lymphoblastic Lymphoma (LBL)
Investigator:	Luke Maese, DO Huntsman Cancer Institute, University of Utah Primary Children's Hospital
Sponsor:	Sponsor's United States Representative: Jazz Pharmaceuticals 3170 Porter Drive Palo Alto, California 94304
Sponsor's Medical Director:	[redacted] MD Executive Medical Director Hematology/Oncology Therapeutic Area Jazz Pharmaceuticals [redacted]
Contract Research Organization:	Pharmaceutical Research Associates, Inc. 4130 Parklake Avenue, Suite 400 Raleigh, North Carolina 27612

Original Protocol Date:	29 August 2019
Amendment 01 Date:	18 August 2020
Amendment 02 Date:	03 September 2020

Confidentiality Statement

This study will be conducted under Good Clinical Practice guidelines.

SYNOPSIS

Sponsor:	Jazz Pharmaceuticals
Product:	Recombinant Crisantaspase *Pseudomonas fluorescens* (RC-P), JZP-458
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
Study Number:	JZP458-201
Study Phase:	2/3
Location:	This study will be conducted globally.
Primary Objectives:	• 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
Key Secondary Objective:	• 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
Secondary Objectives:	• 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
Exploratory Objectives:	• 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

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 will be determined by the occurrence of treatment-emergent adverse events.
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.
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 serum asparaginase activity (SAA) using a population PK approach and exposure-response correlations • Incidence of anti-drug antibody formation against RC-P
Study Design:	This is an open-label, multicenter, dose confirmation, and PK study of RC-P in patients (of any age) with ALL/LBL who are hypersensitive to *E. coli*-derived asparaginases (allergic reaction or silent inactivation). This study is designed to assess the tolerability and efficacy of RC-P (only in patients 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 (IM or IV depending on patient's allocation at study enrollment) will be administered based on each patient's original treatment plan for as long as the patient derives clinical benefit. For patients who complete Course 1, any subsequent scheduled doses of a long-acting *E. coli*-derived asparaginase remaining on the patient's treatment plan will be replaced by 6 doses (6 doses are equivalent to a course) of RC-P until their asparaginase treatment has been completed. 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; study center participation will be at the discretion of the Sponsor. 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. An SDRC Charter will describe the membership of this committee (inclusive of Children's Oncology Group [COG] and Jazz Pharmaceuticals' personnel) and the scope of their actions. **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. **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). Blood samples will be collected for SAA level determination, and other PK/pharmacodynamic (PD) and lab evaluations. 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 the ± 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. 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 (described below in Assessment of Safety/Tolerability in Part A Cohort 1) 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. As described for Cohort 1, Cohort 2 patients will also have the 6 IM 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). Blood samples for SAA level determination as well as other PK/PD and lab evaluations for patients in Part A Cohort 2 will be collected. Safety will be assessed in Part A Cohort 2 by monitoring for and characterizing AEs. 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%. The immunogenicity of IM RC-P will be assessed in Part A Cohort 1 and Cohort 2 of this study. An interim analysis is 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 (ie, the lower bound of the 95% Wald CI for the primary efficacy endpoint exceeds 90%) 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 IM Expansion Cohort may be stopped for safety. If enrollment to this cohort is stopped early, other doses or schedules with RC-P could be considered. If enrollment into this Expansion Cohort continues after the interim analysis, the primary analysis is planned after the 98th patient completes Course 1 of IM RC-P at the final dose level from Part A Cohort 1 and Cohort 2. To further investigate optimal dosing options for patients, evaluation of the asparaginase activity and safety/tolerability of RC-P for the IV route of administration will be conducted as described below. **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 (initial IV starting dose approximately 37.5 mg/m^2 to be determined from a combination of the Phase 1 healthy subject study results and the available Phase 2/3 IM results) 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. Blood samples will be collected for SAA level determination, and other PK/PD and lab evaluations. Additional courses of IV RC-P will be administered based on the patient's original treatment plan for as long as the patient derives clinical benefit; subsequent scheduled doses of a long-acting *E. coli*-derived asparaginase remaining on the patient's treatment plan will be replaced by 6 doses (6 doses are equivalent to a course) of IV RC-P until their asparaginase treatment has been completed.

	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-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 (safety assessed as described for the IM RC-P [Part A] portion of the study) 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. If additional patients at a different dose level are required after the initial Cohort 1a IV RC-P patients, additional subcohorts (Cohort 1b, Cohort 1c…Cohort 1x) for IV dose determination will be evaluated similarly to Cohort 1a to determine the dose for further evaluation. The necessity for additional subcohorts and testing alternate doses of IV RC-P must be based on a review of all of the data. The immunogenicity of IV RC-P will also be assessed in Part B of this study. Note: Dose modifications for individual patients due to possible safety/tolerability issues following the administration of IM or IV RC-P are described in the protocol. **Assessment of Safety/Tolerability by Dose Level in IM RC-P Part A Cohort 1 and IV RC-P Part B Cohort 1** The safety and tolerability of each IM and IV RC-P subcohort will be assessed to determine if enrollment may continue to the Expansion Cohort (Cohort 2). The SDRC will focus on ≥ Grade 3 non-hematologic unanticipated adverse events (AEs). The following AEs **will not** be considered as the single reason to prevent the study from proceeding to Expansion Cohort 2: • Grade 3 fever • Grade 3 or 4 febrile neutropenia or infection • Grade 3 nausea, vomiting or diarrhea that resolves with supportive care to ≤ Grade 2 within 72 hours

	• Grade 3 or 4 alanine aminotransferase (ALT)/aspartate aminotransferase (AST) and/or bilirubin elevation(s) that resolve(s) to ≤ Grade 2 within14 days • Asymptomatic Grade 3 or 4 electrolyte abnormalities correctable with supportive care that resolve to ≤ Grade 2 within 24 hours • Grade 3 hyperglycemia or hypoalbuminemia • Grade 3 or 4 fatigue lasting ≤ 7 days • Grade 3 hypertriglyceridemia that resolves to ≤ Grade 2 within 14 days If the incidence of a clinically significant ≥ Grade 3 non-hematologic unanticipated toxicity (exceptions noted above) exceeds 33% in a subcohort (at n = 6 or n = 13), no further patients will be enrolled at this IM or IV RC-P dose level. The SDRC will recommend if patients being treated at this IM or IV RC-P dose level should continue treatment or if their treatment should be discontinued.
Estimated Overall Duration of Study:	The primary analysis is planned after the 98th patient completes Course 1 of IM RC-P at the final IM RC-P dose level from Part A Cohorts 1 and 2. The overall study (Part A and Part B) will be deemed complete once all enrolled patients have completed all of their planned courses of RC-P, including 30 days of safety follow-up and additional time as needed for follow-up assessments, or discontinued the study early. The final analysis will be conducted at this time. The overall total study duration to complete enrollment and all patient courses, including 30 days of safety follow-up and additional time as needed for follow-up assessments, for Part A (IM) and Part B (IV) at the investigative sites will be approximately 2 years.
Study Population:	The study population will include pediatric and adult patients with ALL or LBL, who have developed a moderate or severe allergic reaction to or have silent inactivation of an *E. coli*-derived asparaginase. **<u>IM RC-P Dose Confirmation (Part A)</u>:** Cohort 1 (Dose Confirmatory) – A target of 13 evaluable patients will be administered 6 doses of the IM RC-P in subcohorts to determine the dose level for Cohort 2. Cohort 2 (Expansion) – Patients will be administered 6 doses of the IM RC-P at the dose level and regimen determined in Cohort 1. Approximately 85 patients are planned to obtain 98 patients in total; 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).

	IV RC-P Dose Confirmation (Part B): A target of at least 6 evaluable patients will be administered 6 doses of RC-P via an IV route of administration to define the optimal dose and schedule of IV RC-P. Once determined, the optimal dose 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.
Eligibility Criteria:	**Inclusion Criteria** Each patient must meet the following criteria to be enrolled in this study: 1. Able to understand and to sign a written informed consent, and/or have their parent or a legally authorized representative sign a written informed consent. Assent, when appropriate, will be obtained according to institutional guidelines. 2. Pediatric and adult patients with a diagnosis of ALL or LBL. 3. Cohort 1 (Part A and Part B): Have had a ≥ Grade 3 allergic reaction (Common Terminology Criteria for Adverse Events [CTCAE] v5.0) to a long-acting *E. coli*-derived asparaginase **OR** have silent inactivation. Cohort 2 ONLY (Part A): Have had a ≥ Grade 2 allergic reaction (CTCAE v5.0) to a long-acting *E. coli*-derived asparaginase **OR** have silent inactivation. For patients with a Grade 2 allergic reaction, SAA testing for inactivation is strongly encouraged. For the purposes of this study, the definition of silent inactivation is as follows: patients with documented NSAA levels as described below at one of the following time points after completion of a long-acting *E. coli*-derived asparaginase infusion (but *without* clinical signs/symptoms of hypersensitivity or allergic reaction): • Time point of 1 hour to 1 day with NSAA < 0.5 IU/mL • Time point of ≤ 7 days with NSAA < 0.3 IU/mL • Time point of ≤ 14 days with NSAA < 0.1 IU/mL 4. Have 1 or more courses of *E. coli*-derived asparaginase (ie, to allow for at least 6 doses of RC-P) remaining in his/her treatment plan. 5. Patients must have, in the opinion of the Investigator, fully recovered from their prior allergic reaction to *E. coli*-derived asparaginase. Patients must have completed antihistamine, epinephrine, and/or corticosteroid treatment for the allergic reaction ≥ 24 hours prior to RC-P administration. Undetectable SAA levels (based on the lower limit of quantification, as defined by a certified laboratory authorized under CLIA [Clinical Laboratory Improvement Amendments] to perform this testing)

	must also be documented prior to enrollment in the study, except for patients who received less than 10% of an *E. coli*-derived asparaginase intravenous infusion prior to the reaction. 6. Have adequate liver function, defined as: direct (conjugated) bilirubin ≤ 3X upper limit of normal (ULN); SGPT (ALT) and SGOT (AST) ≤ 5X ULN. 7. Female subjects of childbearing potential (ie, fertile, following menarche) and male subjects who have female partners of childbearing potential must agree to use medically acceptable methods of contraception with their partners from Screening, throughout the study, and for 30 days after the last dose of RC-P. Medically acceptable methods of contraception that may be used by the subject include abstinence (when this is in line with the preferred and usual lifestyle of the patient), progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action; combination of male condom with either cap, diaphragm, or sponge with spermicide (double barrier methods). **Exclusion Criteria** Patients who meet any of the following criteria will be excluded from the study: 1. Have previously received asparaginase *Erwinia chrysanthemi* or RC-P. 2. Have relapsed ALL or LBL. 3. Are concurrently receiving another investigational agent and/or treated with an investigational device at the same time as RC-P (within 48 hours) during Course 1 of RC-P. 4. Have a history of ≥ Grade 3 pancreatitis (per CTCAE v5.0) 5. Prior history of asparaginase-associated ≥ Grade 3 (per CTCAE v5.0) hemorrhagic event or asparaginase-associated thrombus requiring anticoagulation therapy, excluding catheter-related thrombotic events. 6. Patients who in the opinion of the Investigator may not be able to comply with the efficacy and safety monitoring requirements of the study. 7. Patients who have any serious active disease or co-morbid medical condition (according to Investigator's decision), or psychiatric illness that would prevent the patient from signing the informed consent form, assent form or informed consent form by parents, pending institutional requirements, or per Investigator's opinion, would prevent the patient from completing one course of RC-P.

	8. Pregnant or lactating females or females of childbearing potential not willing to use a medically acceptable of birth control for the duration of the study. Female patients who are lactating and do not agree to stop breast-feeding.
Test Product, Dose, and Mode of Administration:	Recombinant Crisantaspase *Pseudomonas fluorescens* (RC-P) will be administered. 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. Intra-patient dose escalation may be permitted to the next dose level, if applicable, as recommended by the SDRC following review of a dose level. **IM RC-P Dose Confirmation (Part A):** Cohort 1: The starting dose of IM RC-P will be 25 mg/m^2 (based on the results from the Phase 1 study in healthy subjects) with possible subsequent modifications as needed. Subsequent doses will not exceed a 50% increase from the previous dose level. Each Part A Cohort 1 patient will receive at least 6 IM RC-P doses as their first course (Course 1). Cohort 2: The dose level of IM RC-P for Part A Cohort 2 will be informed by data from Part A Cohort 1. **IV RC-P Dose Confirmation (Part B):** Patients will receive an initial dose of IV RC-P (as a 2 hour infusion) with the dose level of approximately 37.5 mg/m^2, initial IV dose selection based on a combination of the Phase 1 healthy subject study results and the available Phase 2/3 IM results.
Duration of Treatment:	The treatment duration for individual patients will vary depending on the number of doses of a long-acting *E. coli*-derived asparaginase remaining on a patient's original treatment protocol (completion of each patient's planned asparaginase treatment). Each patient will be followed for at least 30 days following their last dose of the last course of RC-P.
Efficacy Assessment:	To address the primary objective of the study which is to establish efficacy of RC-P, the primary efficacy endpoint of the study in Part A 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. NSAA levels will be assessed as described under PK Assessments and the protocol schedule of assessments. NSAA levels of ≥ 0.1 IU/mL are well accepted as surrogate markers for adequate asparagine depletion, which correlates with clinical efficacy.

Pharmacokinetic Assessments:	Blood samples for PK analyses will be collected from all patients at pre-specified time points per the sampling schedule (see below), and will be assayed for SAA using a validated method. RC-P must be administered at a different site than the one which will be used for drawing subsequent PK samples. For those patients with a central venous catheter, IV RC-P may be administered via peripheral IV and PK samples will be drawn via a central line. **PK Sampling Schedule** (only the schedule for patients starting RC-P on a **Monday** is included here – the schedule for patients starting on a Wednesday or Friday is provided in the full protocol); *all postdose samples must be collected prior to the subsequent RC-P dose***:** **IM RC-P (Part A), Course 1** (plus or minus the allowable time window)**:** • Dose 1: predose, 2.5 hours (± 15 minutes), and 48 hours postdose (± 2 hours) • Dose 2: 48 hours postdose (± 2 hours) • Dose 3: 72 hours postdose (± 2 hours) • Dose 4: 2.5 hours (± 15 minutes) and 48 hours postdose (± 2 hours) • Dose 5: 48 hours postdose (± 2 hours) **IM RC-P (Part A), Subsequent Courses** (plus or minus the allowable time window)**:** • Dose 1: Predose • Dose 3: 72 hours postdose (± 2 hours) • Dose 5: 48 hours postdose (± 2 hours) • End of Study (if a patient has only 1 course of RC-P, this sample will be collected after Course 1) **IV RC-P (Part B), Course 1 (drug administration is a 2 hour infusion)** (plus or minus the allowable time window)**:** Note: the following time points for sample collection are relative to the start of the RC-P infusion. • Dose 1: predose, end of infusion at 2 hours (+ 15 minutes), and 48 hours postdose (± 2 hours) • Dose 2: 48 hours postdose (± 2 hours) • Dose 3: 72 hours postdose (± 2 hours) • Dose 4: end of infusion at 2 hours (+ 15 minutes) and 48 hours postdose (± 2 hours) • Dose 5: 48 hours postdose (± 2 hours)

	<u>IV RC-P (Part B), Subsequent Courses (drug administration is a 2 hour infusion)</u> (plus or minus the allowable time window)**:** Note: the following time points for sample collection are relative to the start of the RC-P infusion. • Dose 1: Predose • Dose 3: 72 hours postdose (± 2 hours) • Dose 5: 48 hours postdose (± 2 hours) • End of Study (if a patient has only 1 course of RC-P, this sample will be collected after Course 1)
Safety Assessments:	The following safety assessments will be performed during the study: • Adverse events (AEs) • Vital signs • Physical examinations • Clinical laboratory tests All AEs will be graded as per CTCAE version 5.0.
Immunogenicity:	Anti-RC-P antibodies (ADA) will be assessed in this study. Anti-RC-P antibodies will be assessed at predose 1 (prior to the first dose of RC-P), at 48 or 72 hours after Dose 5 during a patient's initial RC-P course, and at the 30 day safety follow-up visit after a patient's final RC-P course (End of Study sample). Anti-RC-P antibodies will be assessed at predose 1 and at the end of the study (as described above) for all subsequent RC-P courses. Additional samples to test for ADA may be obtained if a patient experiences an allergic reaction. If it is determined that a patient has sub-therapeutic NSAA levels (< 0.1 IU/mL), the test for ADA may be performed if there is a blood sample available. In addition, for patients who exhibit positive ADA from samples obtained prior to the end of study (30 days after a patient's final RC-P course), efforts will be made to collect follow-up ADA samples up to approximately 6 months after a patient's last dose of their last course of RC-P. If all required assessments are completed and there is serum remaining from any of the sample types, additional immunogenicity testing may be performed.
Additional Assessments:	Additional assessments will include the measurement of serum asparaginase concentrations (PK content) using a validated enzyme content assay. Additional assessments will also include the measurement of L-asparagine and L-glutamine levels to assess the pharmacodynamic (PD) effect of RC-P blood will be collected for each PD sample from all patients at pre-specified time points including the End of Study time point.

Statistical Methods:	The primary efficacy endpoint of the study is the response rate, defined as the proportion of patients with the last 72-hour NSAA ≥ 0.1 IU/mL, in Course 1 of IM RC-P (Part A). The response rate, along with the 95% Wald CI (confidence interval) will be provided. The primary efficacy endpoint will be met if the lower bound of the 95% CI of the response rate exceeds 90%. The Efficacy Analysis Set will include patients who received at least one dose of RC-P and have at least one 48- or 72-hour NSAA assessment collected within the protocol-defined sample collection window (± 2 hours) in Course 1. The primary efficacy endpoint will be analyzed based on the Efficacy Analysis Set for patients with at least one 72-hour NSAA assessment collected within the protocol-defined sample collection window (± 2 hours) in Course 1 of Part A (Cohort 1 and Cohort 2 patients) at the final IM RC-P dose. The last observed 72-hour NSAA assessment in collected within the protocol-defined sample collection window (± 2 hours) Course 1 will be used in the calculation of the primary efficacy endpoint. The Safety Analysis Set will include patients who received at least one dose of RC-P. The safety analysis will be based on the Safety Analysis Set. The incidence of treatment-emergent AEs for the Safety Analysis Set will be summarized by dose in Part A and Part B. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) to classify events under the primary system organ class and preferred term. The primary analyses of the efficacy and safety endpoints are planned after the 98th patient completes Course 1 at the final IM RC-P dose in Part A (Cohorts 1 and 2). An interim analysis is planned after the 51st patient completes Course 1 at the final IM RC-P dose in Part A (Cohort 1 and Cohort 2 patients). The final analysis will be conducted 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 30 days of safety follow-up and additional time as needed for follow-up assessments, or have discontinued the study early.
Sample Size Considerations:	For Part A (RC-P by IM administration, Cohorts 1 and 2) 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 Repeat Dose/Confirmatory), 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 ≥ 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 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 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. 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. For Part B (RC-P by IV administration, Cohort 1), 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.
Date Amendment 02:	03 September 2020

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations:

ADA	Anti-RC-P antibodies
ADL	Activities of daily living
AE	Adverse event
ALL	Acute lymphoblastic leukemia
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AT-III	Antithrombin III
BLQ	Below limit of quantitation
BSA	Body surface area
CBC	Complete blood count
CEC	Central Ethics Committee
CFR	Code of Federal Regulations
cGMP	current Good Manufacturing Practices
CI	Confidence interval
CLIA	Clinical Laboratory Improvement Amendments
CNS	Central nervous system
COG	Children's Oncology Group
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
DCI	Disseminated intravascular coagulopathy
DMP	Data Management Plan
eCOA	Electronic Clinical Outcome Assessment
E. coli	*Escherichia coli*
eCRF	Electronic case report form
EFS	Event free survival
EMR	Electronic medical record
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
GCP	Good Clinical Practices
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee

Abbreviations:

IgG	Immunoglobulin G
IM	Intramuscular injection
IND	Investigational New Drug
IRB	Institutional Review Board
IRT	Interactive Response Technology
IU	International Unit(s)
IUD	Intrauterine device
IV	Intravenous
kDa	Kilodalton
LAM	Lactational amenorrhoea method
LBL	Lymphoblastic Lymphoma
LMWH	Low molecular weight heparin
MedDRA	Medical Dictionary for Regulatory Activities
mPEG	Monomethoxypolyethylene glycol
MWF	Monday, Wednesday, Friday
NC	North Carolina
NCI	National Cancer Institute
NSAA	Nadir serum asparaginase activity
PD	Pharmacodynamic
PK	Pharmacokinetic
RC-P	Recombinant Crisantaspase produced in *Pseudomonas fluorescens*
REB	Research Ethics Board
SAA	Serum asparaginase activity
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SC	Succinimidyl carbonate
SD	Standard deviation
SDRC	Study Data Review Committee
SOP	Standard Operating Procedures
SS-PEG	polyethylene glycol succinimidyl succinate
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse events
ULN	Upper limit of normal
US	United States (of America)

Abbreviations:

USP	United States Pharmacopeia
WBC	White blood cells

Definitions:

Childbearing Potential =

A woman of childbearing potential (WOCP) is defined as any woman or adolescent who has begun menstruation and is not surgically sterile or post-menopausal. Women who have undergone a hysterectomy, bilateral salpingectomy, or bilateral oophorectomy are considered surgically sterile. Post-menopausal is defined as 12 months of amenorrhea without an alternate medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range (FSH level >40 mIU/mL) may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient (Clinical Trial Facilitation Group 2014).

1. INTRODUCTION

1.1. Background Information and Rationale

The American Cancer Society estimates that approximately 5,930 new cases of acute lymphoblastic leukemia (ALL) will be diagnosed in 2019 in the United States (US), with approximately 60% of these cases occurring in patients < 20 years of age. The risk of developing ALL is highest in children younger than 5 years of age after which the risk gradually decreases until approximately the mid-twenties, increasing slowly again after the age of 50 years. Acute lymphoblastic leukemia is the most frequent cancer occurring in children, accounting for approximately 30% of all childhood cancers (American Cancer Society 2019).

Cellular characteristics and prognostic variables defined by both clinical and laboratory features determine risk groups and risk-based treatments for patients in standard, medium, or high groups (Pulte et al. 2008, Pui et al. 2003). Optimal use of the same anti-leukemic agents that were developed from the 1950s through the 1980s, together with a stringent application of prognostic factors for risk-directed therapy in clinical trials, has resulted in a steady improvement in treatment outcome. In the 1990s, the 5-year, event-free survival rates for childhood ALL generally ranged from 70% to 83% in developed countries with an overall cure rate of approximately 80%. Improved supportive care, more precise risk stratification, and personalized chemotherapy based on the characteristics of the leukemic cells and hosts have pushed the cure rate of childhood acute lymphoblastic leukemia to near 90% (Hunger & Mullighan 2015).

For over 30 years, L-asparaginase (L-asparaginase and asparaginase are used interchangeably within this document) has been an important component of ALL therapy (Pui & Evans 2006). L-asparaginase is currently a standard component of the anti-leukemia armamentarium during the remission induction and consolidation phases, particularly for childhood ALL and is gaining acceptance as part of the ALL therapy in adults (Stock et al. 2008, National Comprehensive Cancer Network 2016). Treatment regimens, especially those including high doses of L-asparaginase, have significantly improved long-term, event-free survival, specifically in children with ALL (Pieters et al. 2011). The incremental survival benefit associated with asparaginase given concomitantly with other chemotherapy has been estimated to be 15% to 20% (Sallan et al. 1983).

L-asparaginase was initially shown to have anti-tumor properties in murine models of lymphoma (Broome 1963, Broome 1981). Normal cells can synthetize L-asparagine via asparagine synthetase, but many malignant cells cannot, due to the lack of L-asparagine synthetase activity and therefore, are dependent on external sources of L-asparagine for RNA and DNA synthesis and viability (Han & Onuma 1972). The dependence of these cells on extrinsic asparagine supplies the rationale for asparaginase treatment.

L-asparaginase hydrolyzes the nonessential amino acid, asparagine, into aspartic acid and ammonia, thus depleting the circulating pool of serum asparagine (Pieters et al. 2011). It is believed that the depletion of plasma levels of L-asparagine by L-asparaginase selectively kills cancer cells, leaving normal cells unaffected. Serum asparaginase activity (SAA) levels serve as a surrogate marker for asparagine depletion, and nadir serum asparaginase activity (NSAA) levels ≥ 0.1 IU/mL are the accepted threshold to demonstrate adequate asparagine depletion in clinical practice (Asselin & Rizzari 2015, Pieters et al. 2011, van der Sluis et al. 2016).

$$\text{L-asparagine} \xrightarrow{\text{L-asparaginase}} \text{L-aspartic acid} + NH_3$$

L-asparaginase is currently used therapeutically in the following preparations: 1) short acting L-asparaginase from *Escherichia coli* (*E. coli*) 2) long-acting *E. coli* L-asparaginase conjugated to 5 kDa monomethoxy polyethylene glycol succinimidyl succinate (SS-PEG), available as Oncaspar® and long-acting *E. coli* L-asparaginase conjugated to monomethoxypolyethylene glycol (mPEG) with a succinimidyl carbonate (SC) linker known as Calaspargase pegol-mknl (Asparlas™), and 3) short acting native *Erwinia chrysanthemi* L-asparaginase (Erwinaze®/Erwinase®), indicated for patients who develop a hypersensitivity reaction to *E. coli*-derived asparaginases.

Because of their bacterial origin, L-asparaginases are highly allergenic and immunogenic, inducing hypersensitivity reactions and the development of high titers of serum immunoglobulin G (IgG) antibodies that may interfere with the therapeutic effect of the enzyme, respectively (Panosyan 2004). The most common toxicity of *E. coli*-derived L-asparaginases is clinical hypersensitivity reactions which are reported in up to one-third of patients receiving intensive schedules of the native forms of the enzyme and less frequently in patients receiving the pegylated form of asparaginase (Raetz & Salzer 2010). However, hypersensitivity reactions remain the most prominent and dose-limiting adverse reactions and there is a clear need for developing immunogenically non-cross reactive preparations.

The inability to receive asparaginase secondary to hypersensitivity has important prognostic implications for patients with ALL. For example, in the Dana Farber Cancer Institute Consortium protocol, DFCI 91-01, asparaginase intolerance (completion of < 25 weeks of planned total of 30 weeks of asparaginase therapy) was associated with significantly worse event-free survival (73% vs 90%, $p < 0.01$) (Silverman et al. 2001). Notably, in the DFCI 00-01 trial individualized dosing of *E. coli* asparaginase produced statistically superior outcome to fixed dosing, with the difference largely explained by patients with silent hypersensitivity (neutralization of serum asparaginase activity without clinical symptoms of hypersensitivity) in the individualized dose arm who were switched to alternate asparaginase preparations while those in the fixed dose arm continued to receive *E. coli* asparaginase (Vrooman et al. 2013).

The benefit of intensive asparaginase treatment compared with less intensive regimens has been demonstrated in numerous additional studies (Amylon et al. 1999, Moghrabi et al. 2007, Pession et al. 2005). In addition, many patients are not receiving their complete asparagine depleting therapy due to hypersensitivity reactions, the negative effects of which were demonstrated in a recent publication (Gupta et al. 2019). This analysis examined over 8,000 patients enrolled on two historical Children's Oncology Group (COG) trials of patients with ALL and found a significantly inferior event free survival (EFS) in all high risk and slow early responding standard risk patients with ALL who did not complete their prescribed courses of asparaginase. Therefore, to ensure that patients who develop dose-limiting hypersensitivity to *E. coli*-derived asparaginase products receive an adequate therapeutic course, similar alternative preparations are warranted.

A recombinant crisantaspase (such as Recombinant Crisantaspase produced in *Pseudomonas fluorescens*) with no immunological cross-reactivity to *E. coli*-derived asparaginase would address a significant medical need (as a component of a multi-agent chemotherapeutic regimen)

for patients with ALL/Lymphoblastic Lymphoma (LBL), by helping to ensure availability of an asparaginase for patients who have developed hypersensitivity to *E. coli*–derived asparaginase.

1.2. Prior Studies

Analytical comparability studies demonstrate that the new Recombinant Crisantaspase produced in *Pseudomonas fluorescens* (RC-P) is highly similar to asparaginase *Erwinia chrysanthemi* which is purified from a different host. Preliminary results from the RC-P Phase 1 study (JZP458-101) in healthy subjects demonstrated that the majority of the subjects had SAA levels ≥ 0.1 IU/mL at 72 hours after one dose of RC-P administered intramuscularly (IM) or intravenously (IV).The Investigator should refer to the RC-P Investigator's Brochure (IB) for information regarding RC-P.

1.3. RC-P Potential Risks

Potential risks to patients treated with RC-P are similar to those for other asparaginases. Adverse events of interest for asparaginases in general may include events involving allergic reactions of any type (including hypersensitivity), pancreatitis, hyperglycemia, elevated transaminases, and clinical coagulation abnormalities.

In the Phase 1 healthy volunteer study recently conducted with RC-P there were no deaths, no serious adverse events (SAEs), no ≥ Grade 3 adverse events (AEs), and no withdrawals from the study.

The most common treatment emergent AEs determined to be related to RC-P by the Investigator were nausea, vomiting, and dyspepsia. No unanticipated AEs of interest for the administration of RC-P were reported in this study with healthy adults.

1.4. Justification for Dosage and Route of Administration

A Phase 1 study (JZP458-101) was conducted in healthy adult subjects to evaluate the safety, tolerability, and pharmacokinetics (PK) of IM and IV administrations of RC-P. The Phase 1 study starting dose for RC-P dose cohort 1 for both the IM and IV routes of administration was 25 mg/m^2. The RC-P second dose cohort enrolled additional healthy subjects, where the IM dose was 12.5 mg/m^2 and the IV dose was 37.5 mg/m^2.

All dose levels of RC-P were well tolerated in subjects in this Phase1 study; there were no unanticipated AEs, no Grade 3 or higher AEs, and no SAEs. The safety profile observed was consistent with other asparaginases.

Serum asparaginase activity (SAA) levels serve as a surrogate marker for asparagine depletion, and NSAA levels ≥ 0.1 IU/mL are the accepted threshold to demonstrate adequate asparagine depletion in clinical practice. The Phase 1 study SAA results were:

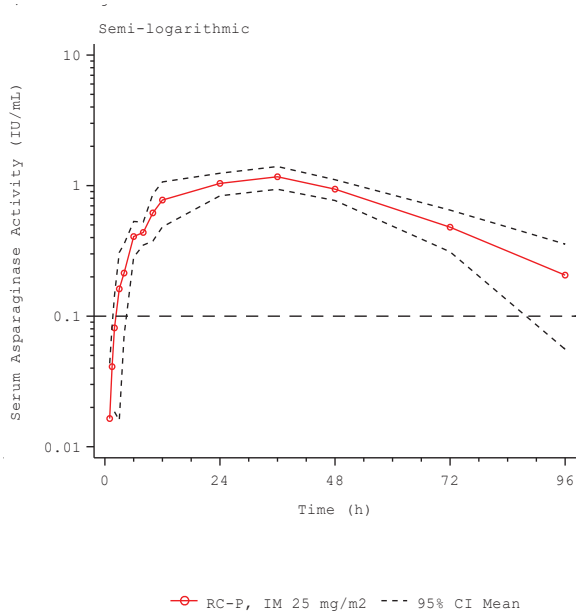
- following IM RC-P administration in subjects, SAA values achieved were greater than 0.1 IU/mL in 6/6 subjects at 72 hours postdose for the 12.5 and 25 mg/m^2 dose levels
- following IV RC-P administration in subjects, SAA values achieved were greater than 0.1 IU/mL in 4/6 subjects at 72 hours postdose at the dose level of 25 mg/m^2 while 6 out

of 6 subjects achieved greater than 0.1 IU/mL at 72 hours postdose at the dose level of 37.5 mg/m^2

Based on the Phase 1 PK (72 hour NSAA levels ≥ 0.1 IU/mL) and safety data, the starting dose for the Phase 2/3 will be 25 mg/m^2 for the IM route of administration and 37.5 mg/m^2 is the proposed starting dose for the IV route of administration. Semi-logarithmic figures for the mean (95% CI) SAA time profiles for IM RC-P 25 mg/m^2 (Figure 1) and IV RC-P 37.5 mg/m^2 (Figure 2) are provided from the Phase 1 study results. The dosing schedule for each course of RC-P will be based on a Monday, Wednesday, Friday (MWF) schedule with the option for the first dose of RC-P to start on Monday, Wednesday, or Friday. The RC-P IB provides further information from the Phase 1 study.

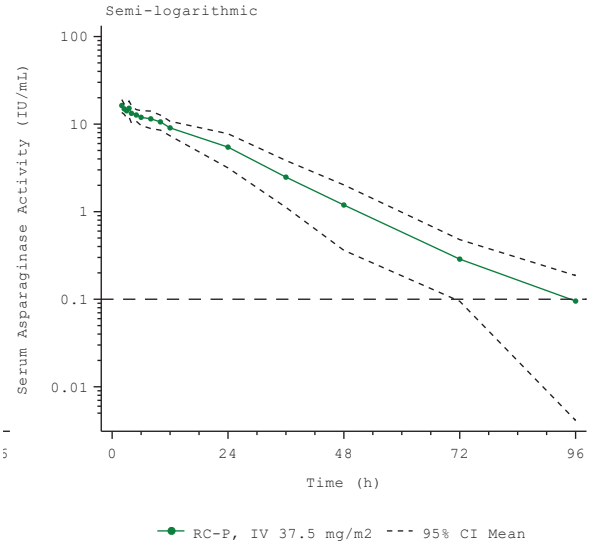
Any additional dose level(s) studied for RC-P will not exceed a 50% increase from the previous dose level.

Figure 1: JZP458-101 Study: Mean (95% CI) Serum Asparaginase Activity-Time Profiles for IM RC-P 25 mg/m^2



Note: Lower limit of quantitation = 0.0250 IU/mL; values below the lower limit of quantitation were set to zero.
Abbreviations: CI = confidence interval; IM = intramuscular; IU = International Units;
Source: Figure 14.2.1.5 22July2019

Figure 2: JZP458-101 Study: Mean (95% CI) Serum Asparaginase Activity-Time Profiles for IV RC-P 37.5 mg/m^2



Note: Lower limit of quantitation = 0.0250 IU/mL; values below the lower limit of quantitation were set to zero.
Abbreviations: CI = confidence interval; IV = intravenous; IU = International Units;
Source: Figure 14.2.1.5 22July2019

1.5. Compliance Statement

This study will be conducted in compliance with this protocol, Good Clinical Practice (GCP), and applicable regulatory requirements.

Sponsor signatures indicating approval of this protocol are provided in Appendix 4.

2. STUDY OBJECTIVES/ENDPOINTS

2.1. Study Objectives

2.1.1. Primary Objectives

- To determine the efficacy of IM RC-P administration as measured by the response in Cohort 1 and Cohort 2, defined as the last 72-hour 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

2.1.2. Key Secondary Objective

- 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

2.1.3. Secondary Objectives

- 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 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

2.1.4. Exploratory Objectives

- To determine the efficacy of 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

2.2. Study Endpoints

2.2.1. 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 will be determined by the occurrence of treatment-emergent adverse events.

2.2.2. 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.

2.2.3. 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 formation against RC-P

2.2.4. 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
- Incidence of anti-drug antibody formation against RC-P

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design

This is an open-label, multicenter, dose confirmation, and PK study of RC-P in patients (of any age) with ALL/LBL who are hypersensitive to *E. coli*-derived asparaginases (allergic reaction or silent inactivation). This study is designed to assess the tolerability and efficacy of RC-P (only in patients 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 (IM or IV depending on patient's allocation at study enrollment) will be administered based on each patient's original treatment plan for as long as the patient derives clinical benefit. For patients who complete Course 1, subsequent scheduled doses of a long-acting *E. coli*-derived asparaginase remaining on the patient's treatment plan will be replaced by 6 doses (6 doses are equivalent to a course) of RC-P until their asparaginase treatment has been completed. Dose modifications for individual patients due to possible safety/tolerability issues following the administration of IM or IV RC-P are described in Section 5.5.

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; study center participation will be at the discretion of the Sponsor. Each course (6 doses) of RC-P dosing may start on either a Monday, Wednesday, or a Friday (Table 1).

Efficacy and safety data will be assessed by a Study Data Review Committee (SDRC) at frequent intervals as described below. The membership of this SDRC will include Children's Oncology Group (COG) and Jazz Pharmaceuticals' personnel. The SDRC will make recommendations and have oversight of the study as described in Section 9.6 and detailed in 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.

Table 1: Overview of Each Study Course - Part A (IM) and Part B (IV) Cohorts

Monday Start:

Part A (IM) Cohorts 1 & 2	**Dose 1 (Mon)**	**Dose 2 (Wed)**	**Dose 3 (Fri)**
Week 1	RC-P	RC-P	RC-P
	Dose 4 (Mon)	**Dose 5 (Wed)**	**Dose 6 (Fri)**
Week 2	RC-P	RC-P	RC-P
Part B (IV) Cohort 1	**Dose 1 (Mon)**	**Dose 2 (Wed)**	**Dose 3 (Fri)**
Week 1	RC-P	RC-P	RC-P
	Dose 4 (Mon)	**Dose 5 (Wed)**	**Dose 6 (Fri)**
Week 2	RC-P	RC-P	RC-P

Wednesday Start:

Part A (IM) Cohorts 1 & 2		**Dose 1 (Wed)**	**Dose 2 (Fri)**
Week 1		RC-P	RC-P
	Dose 3 (Mon)	**Dose 4 (Wed)**	**Dose 5 (Fri)**
Week 2	RC-P	RC-P	RC-P
	Dose 6 (Mon)		
Week 3	RC-P		
Part B (IV) Cohort 1		**Dose 1 (Wed)**	**Dose 2 (Fri)**
Week 1		RC-P	RC-P
	Dose 3 (Mon)	**Dose 4 (Wed)**	**Dose 5 (Fri)**
Week 2	RC-P	RC-P	RC-P
	Dose 6 (Mon)		
Week 3	RC-P		

Friday Start:

Part A (IM) Cohorts 1 & 2			**Dose 1 (Fri)**
Week 1			RC-P
	Dose 2 (Mon)	**Dose 3 (Wed)**	**Dose 4 (Fri)**
Week 2	RC-P	RC-P	RC-P
	Dose 5 (Mon)	**Dose 6 (Wed)**	
Week 3	RC-P	RC-P	
Part B (IV) Cohort 1			**Dose 1 (Fri)**
Week 1			RC-P
	Dose 2 (Mon)	**Dose 3 (Wed)**	**Dose 4 (Fri)**
Week 2	RC-P	RC-P	RC-P
	Dose 5 (Mon)	**Dose 6 (Wed)**	
Week 3	RC-P	RC-P	

3.1.1. IM RC-P (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 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 the 6 IM 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). Blood samples will be collected for SAA level determination, and other PK/pharmacodynamic (PD) and lab evaluations as described (Section 6). The starting dose for RC-P Dose Cohort 1a will be 25 mg/m^2 (justification is provided in Section 1.4). Additional subcohorts (eg, Cohort 1b, Cohort 1c… Cohort 1x) may be opened to determine the optimal dose for Cohort 2 (see Section 3.1.3.1).

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 the ± 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.

The SDRC will review the data when 6 evaluable patients in each subcohort complete Course 1 and when 13 evaluable patients in each subcohort complete Course 1. The evaluation and necessity for additional patients/cohorts is described in Section 3.1.3.1 and Figure 3. Any additional dose level(s) studied for RC-P will not exceed a 50% increase from the previous dose level.

Any subsequent scheduled doses of a long-acting *E. coli*-derived asparaginase remaining on the patient's treatment plan will be replaced by 6 doses (1 course) of IM RC-P until their asparaginase treatment has been completed.

Details of the study assessments and procedures are presented in Appendix 1.

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.

As described for Cohort 1, Cohort 2 patients will also have the 6 IM 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). Blood samples for SAA level determination for patients in Part A Cohort 2 will be collected as described under PK assessments (Section 6.4). Safety will be assessed in Part A Cohort 2 by monitoring for and characterizing AEs.

The SDRC will review the data on NSAA levels at frequent intervals for Cohort 2 (see Section 9.6); 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%.

An interim analysis is planned after the 51st patient completes Course 1 with the final IM RC-P dose level (Cohort 1 plus Cohort 2 patients). If the primary endpoint is met (ie, the lower bound of 95% Wald CI for the primary efficacy endpoint exceeds 90%) 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 IM Expansion Cohort may be stopped for safety. If enrollment to this cohort is stopped early, other doses or schedules with RC-P could be considered.

If enrollment into Cohort 2 (Expansion) continues after the interim analysis, the primary analysis is planned after the 98th patient completes Course 1 of IM RC-P at the final IM RC-P dose level from Part A Cohorts 1 and 2. The primary endpoint of the study will be 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 in **Part A** Cohort 1 and Cohort 2. Safety and tolerability evaluations will also be assessed by the occurrence of treatment-emergent adverse events (TEAEs).

3.1.2. IV RC-P (Part B)

To further investigate optimal dosing options for patients, evaluation of the asparaginase activity and safety/tolerability of RC-P for the IV route of administration will be conducted in Part B of the study as described below.

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 IV administration of RC-P (initial IV starting dose of 37.5 mg/m^2; Section 1.4) 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) as described below and in Section 3.1.3.2 and Figure 4.

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. Blood samples will be collected for SAA level determination, and other PK/PD and lab evaluations as described (Section 6).

Additional courses of IV RC-P will be administered based on the patient's original treatment plan for as long as the patient derives clinical benefit; subsequent scheduled doses of a long-

acting *E. coli*-derived asparaginase remaining on the patient's treatment plan will be replaced by 6 doses (6 doses are equivalent to a course) of IV RC-P until their asparaginase treatment has been completed.

After all required patients in a cohort are enrolled and treated with 6 doses of IV RC-P, the dose level will be evaluated and the necessity for additional patients/cohort (Cohort 1b) will be determined by the SDRC based on the criteria described in Section 3.1.3.2.

Details of the study assessments and procedures are presented Appendix 1.

3.1.3. Possible Scenarios for Dosing Cohorts

The possible scenarios for the expansion of a cohort or opening of new dose cohorts for Part A (IM) and Part B (IV) are summarized in Figure 3 and Figure 4, respectively and are further described in the sections below.

3.1.3.1. Part A (IM) Cohort 1, Determination for Possible Additional Patients/Cohorts

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 the ± 2-hour window) during the second half of Course 1. For patients who are treated but are not evaluable, additional patients may be enrolled.

The SDRC (Section 9.6) will review the data when 6 evaluable patients in each subcohort (ie, Cohort 1a, Cohort 1b, Cohort 1c…Cohort 1x) 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 (described in Section 3.1.3.3 Assessment of Safety/Tolerability in Part A Cohort 1) 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.

3.1.3.2. Part B (IV), Determination for Possible Additional Cohorts

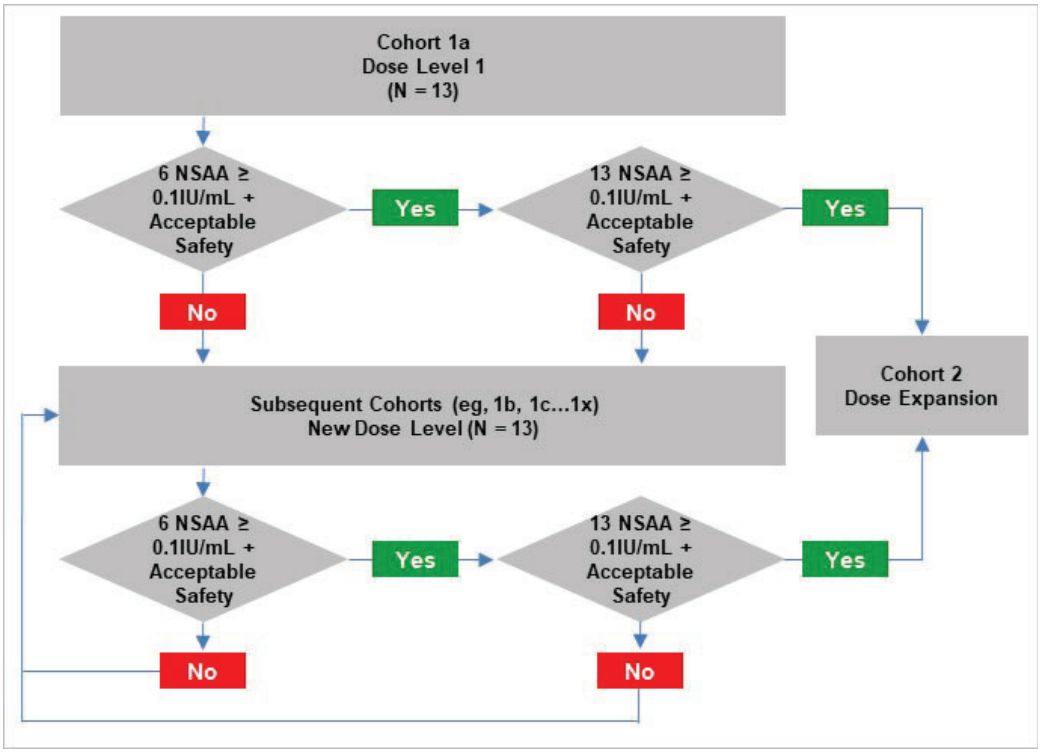
A target of at least 6 evaluable patients will be enrolled in Cohort 1a at a starting dose of 37.5 mg/m^2; more patients may be enrolled as described below. Evaluable patients for Cohort 1 are defined as patients who have received at least 3 doses of IV RC-P and have a 72-hour NSAA level (obtained within the ± 2-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 (safety assessed as described for the IM RC-P [Part A] portion of the study in Section 3.1.3.3) 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.

However, if additional patients at a different dose level are required after the initial Cohort 1a IV RC-P patients, additional subcohorts (Cohort 1b, Cohort 1c…Cohort 1x) for IV dose determination will be evaluated similarly to Cohort 1a to determine the dose for further evaluation. The necessity for additional subcohorts and testing alternate doses of IV RC-P must be based on a review of all of the data. Any additional dose level(s) studied for RC-P will not exceed a 50% increase from the previous dose level.

Figure 3: Part A IM RC-P Dose Cohorts

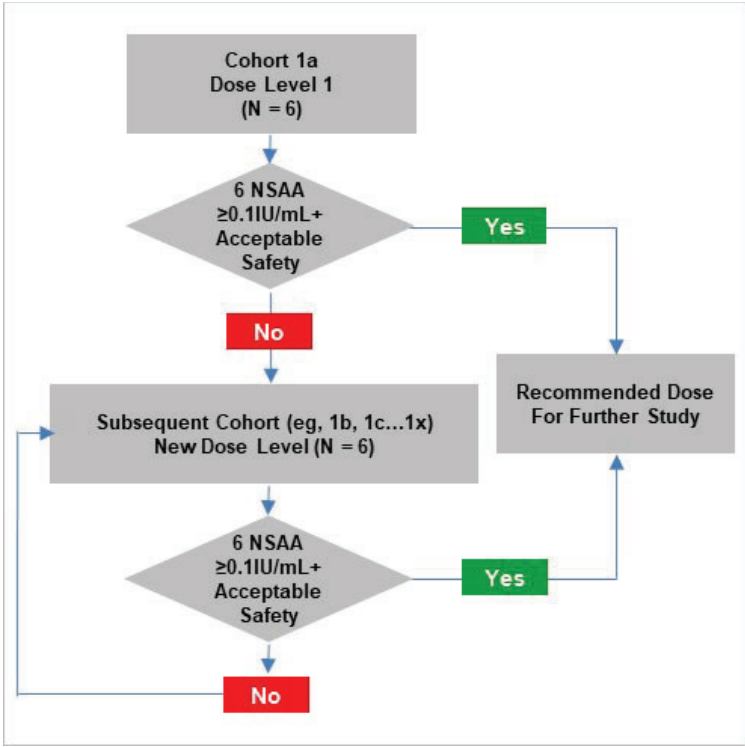


Note: The SDRC will assess the safety and tolerability issues for patients in Cohort 1 to determine if additional patients at different dose levels are needed or if the appropriate IM RC-P dose level to proceed to the Expansion Cohort (Cohort 2) has been determined (Section 3.1.3.1.)

Note: The SDRC will review NSAA and safety/tolerability data when 6 and 13 evaluable patients in each subcohort complete Course 1; enrollment will not stop at the specified time points for SDRC review.

Abbreviations: IM = intramuscular; IU = International Units; NSAA = nadir serum asparaginase activity; SDRC = Study Data Review Committee

Figure 4: Part B IV RC-P Dose Cohorts



Notes: The SDRC will assess the safety and tolerability issues for patients in Cohort 1 to determine if additional patients at a different dose level are needed. The SDRC will review NSAA and safety/tolerability data when 6 evaluable patients in each subcohort complete Course 1.

Abbreviations: IU = International Units; IV = intravenous; NSAA = nadir serum asparaginase activity; SDRC = Study Data Review Committee

3.1.3.3. Assessment of Safety/Tolerability by Subcohort in IM RC-P Part A Cohort 1 and IV RC-P Part B Cohort 1

The safety and tolerability of each IM and IV RC-P subcohort will be assessed to determine if enrollment may continue to the Expansion Cohort (Cohort 2). The SDRC will focus on ≥ Grade 3 non-hematologic unanticipated AEs. The following AEs **will not** be considered as the single reason to prevent the study from proceeding to Expansion Cohort 2:

- Grade 3 fever
- Grade 3 or 4 febrile neutropenia or infection
- Grade 3 nausea, vomiting or diarrhea that resolves with supportive care to ≤ Grade 2 within 72 hours
- Grade 3 or 4 alanine aminotransferase (ALT)/aspartate aminotransferase (AST) and/or bilirubin elevation(s) that resolve(s) to ≤ Grade 2 within14 days
- Asymptomatic Grade 3 or 4 electrolyte abnormalities correctable with supportive care that resolve to ≤ Grade 2 within 24 hours
- Grade 3 hyperglycemia or hypoalbuminemia
- Grade 3 or 4 fatigue lasting ≤7 days
- Grade 3 hypertriglyceridemia that resolves to ≤ Grade 2 within 14 days

If the incidence of a clinically significant ≥ Grade 3 non-hematologic unanticipated toxicity (exceptions noted above) exceeds 33% in a subcohort (at n = 6 or n = 13), no further patients will be enrolled at this IM or IV RC-P dose level. The SDRC will recommend if patients being treated at this IM or IV RC-P dose level should continue treatment or if their treatment should be discontinued.

3.2. Rationale for Study Design

This pivotal Phase 2/3 study is designed to assess the safety, tolerability, and efficacy of repeated doses of IM RC-P in patients with ALL/LBL who are hypersensitive to *E. coli*-derived asparaginases and to identify a dose level of IV RC-P for further evaluation. The results of the trial will support the safety, tolerability, and efficacy of the recommended dose for IM administration.

3.3. Number of Patients

For Part A (RC-P by IM administration, Cohorts 1 and 2) of the study, approximately 98 patients (combining Cohorts 1 and 2) are planned at the final IM RC-P dose level; if additional dose levels are necessary to obtain the desired NSAA level/response, additional patients will be enrolled in Part A.

- Cohort 1 (Dose Confirmatory) – A target of 13 evaluable patients will be administered 6 doses of the IM RC-P in subcohorts to determine the dose level for Cohort 2. The starting dose for the first Cohort 1 subcohort (Cohort 1a) will be 6 doses at 25 mg/m^2 each, which was the dose determined from the Phase 1 healthy subject study.

- Cohort 2 (Expansion) – Patients will be administered 6 doses of the IM RC-P at the dose level and regimen determined in Cohort 1. Approximately 85 patients are planned to obtain 98 patients; 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).

For Part B (RC-P by IV administration, Cohort 1), a target of at least 6 evaluable patients will be administered 6 doses of RC-P via an IV route of administration to define the optimal dose and schedule of IV RC-P. Once determined, the optimal dose 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.

3.4. Study Duration

The treatment duration for individual patients will vary depending on the number of doses of a long-acting *E. coli*-derived asparaginase remaining on a patient's original treatment protocol (completion of each patient's planned asparaginase treatment). Each patient will be followed for at least 30 days following their last dose of the last course of RC-P. If an individual patient has one course of RC-P their study duration will be approximately 72 days (including a Screening period of up to 28 days, one course of treatment [6 doses of treatment over a 2 week period], and a follow-up assessment for safety occurring 30 days after the patient's last dose in their last course of RC-P). 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; subsequent scheduled doses of a long-acting *E. coli*-derived asparaginase remaining on the patient's treatment plan will be replaced by 6 doses (6 doses are equivalent to a course) until their asparaginase treatment has been completed.

The overall study (Part A and Part B) will be deemed complete once all enrolled patients have completed all of their planned courses of RC-P, including 30 days of safety follow-up and additional time as needed for follow-up assessments, or discontinued the study early. The final analysis will be conducted at this time (see Section 8 for descriptions of the possible analyses [interim, primary, and final]).

The overall total study duration to complete enrollment and all patient courses, including 30 days of safety follow-up and additional time as needed for follow-up assessments, for Part A (IM) and Part B (IV) at the investigative sites will be approximately 2 years.

4. SELECTION OF STUDY POPULATION

This study will be conducted globally.

4.1. Patient Inclusion Criteria

Each patient must meet all of the following criteria to be enrolled in the study:

1. Able to understand and to sign a written informed consent, and/or have their parent or a legally authorized representative sign a written informed consent. Assent, when appropriate, will be obtained according to institutional guidelines.
2. Pediatric and adult patients with a diagnosis of ALL or LBL.
3. Cohort 1 (Part A and Part B): Have had a ≥ Grade 3 allergic reaction (Common Terminology Criteria for Adverse Events [CTCAE] v5.0) to a long-acting *E. coli*-derived asparaginase **OR** have silent inactivation.

   Cohort 2 ONLY (Part A): Have had a ≥ Grade 2 allergic reaction (CTCAE v5.0) to a long-acting *E. coli*-derived asparaginase **OR** have silent inactivation. For patients with a Grade 2 allergic reaction, SAA testing for inactivation is strongly encouraged.

   For the purposes of this study, the definition of silent inactivation is as follows: patients with documented NSAA levels as described below at one of the following time points after completion of a long-acting *E. coli*-derived asparaginase infusion (but without clinical signs/symptoms of hypersensitivity or allergic reaction):

   - Time point of 1 hour to 1 day with NSAA < 0.5 IU/mL
   - Time point of ≤ 7 days with NSAA < 0.3 IU/mL
   - Time point of ≤ 14 days with NSAA < 0.1 IU/mL
4. Have 1 or more courses of *E. coli*-derived asparaginase (ie, to allow for at least 6 doses of RC-P) remaining in his/her treatment plan.
5. Patients must have, in the opinion of the Investigator, fully recovered from their prior allergic reaction to *E. coli*-derived asparaginase. Patients must have completed antihistamine, epinephrine, and/or corticosteroid treatment for the allergic reaction ≥ 24 hours prior to RC-P administration. Undetectable SAA levels (based on the lower limit of quantification, as defined by a certified laboratory authorized under CLIA [Clinical Laboratory Improvement Amendments] to perform this testing) must also be documented prior to enrollment in the study, except for patients who received less than 10% of an *E. coli*-derived asparaginase intravenous infusion prior to the reaction.
6. Have adequate liver function, defined as: direct (conjugated) bilirubin ≤ 3X upper limit of normal (ULN); SGPT (ALT) and SGOT (AST) ≤ 5X ULN.
7. Female subjects of childbearing potential (ie, fertile, following menarche) and male subjects who have female partners of childbearing potential must agree to use medically acceptable methods of contraception with their partners from Screening, throughout the study, and for 30 days after the last dose of RC-P. Medically acceptable methods of contraception that may be used by the subject include abstinence (when this is in line with the preferred and usual lifestyle of the patient), progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action;

combination of male condom with either cap, diaphragm, or sponge with spermicide (double barrier methods).

4.2. Patient Exclusion Criteria

Patients who meet any of the following criteria will be excluded from the study:

1. Have previously received asparaginase *Erwinia chrysanthemi* or RC-P.
2. Have relapsed ALL or LBL.
3. Are concurrently receiving another investigational agent and/or treated with an investigational device at the same time as RC-P (within 48 hours) during Course 1 of RC-P.
4. Have a history of ≥ Grade 3 pancreatitis (per CTCAE v5.0).
5. Prior history of asparaginase-associated ≥ Grade 3 (per CTCAE v5.0) hemorrhagic event or asparaginase-associated thrombus requiring anticoagulation therapy, excluding catheter-related thrombotic events.
6. Patients who in the opinion of the Investigator may not be able to comply with the efficacy and safety monitoring requirements of the study.
7. Patients who have any serious active disease or co-morbid medical condition (according to Investigator's decision), or psychiatric illness that would prevent the patient from signing the informed consent form, assent form or informed consent form by parents, pending institutional requirements, or per Investigator's opinion, would prevent the patient from completing one course of RC-P.
8. Pregnant or lactating females or females of childbearing potential not willing to use a medically acceptable of birth control for the duration of the study. Female patients who are lactating and do not agree to stop breast-feeding.

4.3. Contraception Recommendations

Female patients (and female partners of male patients) of childbearing potential (ie, fertile/following menarche; see full definition in List of Abbreviation and Definitions of Terms) who are sexually active must agree to use medically acceptable methods of contraception with their partners during exposure to RC-P and for 30 days after a patient's last dose of the last course of RC-P.

Medically acceptable methods of contraception that may be used by the subject include abstinence (when this is in line with the preferred and usual lifestyle of the patient), progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action; combination of male condom with either cap, diaphragm, or sponge with spermicide (double barrier methods). Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, single barrier methods (male or female condom with or without spermicide; cap, diaphragm or sponge with spermicide) and lactational amenorrhoea method (LAM) are not acceptable methods of contraception for this study. Female condoms and male condoms should not be used together.

5. STUDY TREATMENTS

5.1. Description of Study Treatments

5.1.1. RC-P

Recombinant Crisantaspase produced in *Pseudomonas fluorescens* (RC-P) is an L-asparaginase with a highly comparable structure to that of asparaginase *Erwinia chrysanthemi*; RC-P is expressed in *Pseudomonas fluorescens* as a tetramer consisting of four identical subunits, each having a molecular weight of about 35 kilodaltons (kDa).Specific activity is expressed in U/mg, which is defined as the amount of enzyme that catalyses the conversion of 1 µmol of L-asparagine (equivalent to 1 µmol of ammonia produced) per reaction minute, per mg of protein; this is measured by the product specific activity assay.

The RC-P drug product is supplied as a clear to opalescent, slightly brown-yellow or slightly yellow, sterile solution. The product is filled into Type 1 borosilicate glass vials to a 0.5 mL nominal fill volume. Each vial of RC-P drug product contains 10 mg of recombinant crisantaspase in a stable liquid formulation containing sodium phosphate, trehalose, sodium chloride, and polysorbate 80 at target pH of 7.0. Additional details are provided in the RC-P IB.

5.2. Study Treatment Dosages

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. For institutions where BSA is not calculated by an existing algorithm in the electronic medical record (EMR), the calculation of BSA should be performed using the Mosteller formula as follows:

Metric units: $BSA\ (m^2) = ([Height\ (cm) \times Weight\ (kg)] / 3600)^{½}$

Non-metric units (US): $BSA\ (m^2) = ([Height\ (in) \times Weight\ (lb)] / 3131)^{½}$

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. Intra-patient dose escalation may be permitted to the next dose level, if applicable, as recommended by the SDRC following review of a dose level.

IM RC-P Dose Confirmation (Part A):

In Part A of the study, RC-P will be administered via the IM route (prepared and administered as described in Study Pharmacy Manual). For **IM RC-P Dose Cohort 1**, the starting dose of RC-P will be 25 mg/m^2 (see Section 1.4 for justification) with 6 IM 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. Appendix 1 provides the RC-P dosing schedule by the dose start day (Monday, Wednesday, and Friday). Additional IM RC-P cohorts may be enrolled based on the criteria in Section 3.1.3.1 as determined by the Sponsor with guidance from the SDRC. The amount a dose may be increased is also described in Section 3.1.3.1.

For IM administration, the volume of RC-P at a single injection site should be limited to 2 mL with the use of multiple injection sites if needed.

IV RC-P Dose Confirmation (Part B):

In Part B of the study, RC-P will be administered via the IV route (prepared and administered as described in Study Pharmacy Manual). For **IV RC-P Dose Cohort 1**, the starting dose of RC-P is planned to be 37.5 mg/m^2 (see Section 1.4 for justification). Additional IV RC-P cohorts may be enrolled based on the criteria in Section 3.1.3.2 as determined by the SDRC. The additional IV dose levels that may be explored will be based on the information as also described in Section 3.1.3.2.

Administration of IV RC-P should be commenced within 4 hours of preparation; the IV infusion should be administered over 2 hours. Material not used within this timeframe should be discarded. While the infusion is ongoing, other IV drugs should not be administered through the same IV line.

5.3. Timing of RC-P Dose

Prior to administration of RC-P, patients must have fully recovered from their prior allergic reaction to an *E. coli*-derived asparaginase and have documented undetectable SAA levels (based on the lower limit of quantification, as defined by a certified laboratory authorized under CLIA to perform this testing). If a patient has received < 10% of an *E. coli*-derived asparaginase infusion, undetectable SAA levels will not need to be documented prior to administration of RC-P.

5.4. Method of Assigning Patients to Treatments

This is an open-label study with only one study treatment (RC-P).

5.5. Dose Modifications for Safety/Tolerability Issues

5.5.1. Systemic Allergic Reaction/Anaphylaxis

- Discontinue RC-P if the patient develops ≥ Grade 3 allergic reaction/hypersensitivity

5.5.2. Disseminated Intravascular Coagulopathy (DIC)

- If ≥ Grade 3 symptomatic, hold RC-P until symptoms resolve, then resume with the next scheduled dose. Consider factor replacement (fresh frozen plasma, cryoprecipitate, factor VIIa). Do not withhold dose for abnormal laboratory findings without clinical symptoms.

5.5.3. Hyperbilirubinemia

- RC-P dose may need to be withheld depending on a patient's direct bilirubin level as shown in Table 2.

Table 2: RC-P Dose Modifications for Hyperbilirubinemia

Direct Bilirubin Level	RC-P Dose Modification
≤ 3.0 mg/dL	Full dose
3.1 – 5.0 mg/dL	Hold dosing and resume when direct bilirubin is < 2 mg/dL
> 5.0 mg/dL	Discontinue RC-P dosing

Per dosing modifications for hyperbilirubinemia recommended for asparaginases

5.5.4. Hyperglycemia

- Do not modify the dose of RC-P; treat hyperglycemia as medically indicated

5.5.5. Hyperlipidemia

- Do not modify the dose of RC-P; treat hyperlipidemia as medically indicated

5.5.6. Pancreatitis

- Discontinue RC-P in the presence of Grade 3 or Grade 4 pancreatitis. In the case of asymptomatic Grade 2 pancreatitis (enzyme elevation or radiographic findings only), RC-P should be held until amylase/lipase levels return to normal and/or other signs subside, and then resumed.

5.5.7. Thrombosis (including CNS and non-CNS events)

- Withhold RC-P until acute symptoms resolve and treat with appropriate antithrombotic therapy and consider repletion of antithrombin III (AT-III), as indicated. Upon resolution of symptoms, consider resuming RC-P while continuing low molecular weight heparin (LMWH) or antithrombotic therapy. Consider measurement and repletion of AT-III during subsequent courses of RC-P if unable to achieve therapeutic Anti-Xa levels. For significant thrombosis (not catheter-related) consider evaluation for inherited predisposition to thrombosis. Do not modify RC-P dose for a catheter-related thrombotic event.

5.6. Allocation of Study Drug

At confirmation of eligibility, patients will be assigned a patient number in the order in which they are enrolled in the study through an Interactive Response Technology (IRT) system. As identified within the cohort assignment, the patient number will be associated with the allocation of treatment.

5.7. Blinding

This is an open-label study; therefore, there will be no blinding.

5.8. Prior, Concomitant, and Prohibited Medications

5.8.1. Prior and Concomitant Medications

A patient's chemotherapy (other than the addition of RC-P) will continue according to the therapeutic regimen as defined in the patient's original treatment protocol for the patient's

ALL/LBL. All medications and therapies taken by the patient within 14 days prior to Screening and until the final scheduled safety follow-up visit (30 days after their last dose of the last course of RC-P) will be recorded.

5.8.2. Prohibited Medications

Patients should not receive other investigational agents and/or be treated with investigational devices at the same time as RC-P (within 48 hours) during Course 1 of RC-P. There are no restrictions regarding investigational agents/devices for subsequent RC-P courses (ie, after Course 1).

5.9. Treatment Compliance

Study drug will be administered by study site personnel at the investigative site. Treatment compliance will be monitored by recording the exact time of end of injection (IM administration) of study drug or the exact times of the start and end of infusion (IV administration).

5.10. Study Drug Packaging, Labeling, and Dispensing

Study drug will be provided to each study site by Jazz Pharmaceuticals or designee. Each single RC-P vial contains 10 mg of recombinant crisantaspase with a deliverable volume of 0.5 mL of asparaginase activity. All packaging and labeling operations will be performed according to current Good Manufacturing Practices (cGMP) and GCP.

Study drug will be dispensed by qualified clinical personnel (eg, site pharmacist or designee) at the clinical site in accordance with the cohort assignments for the study. The Investigator and/or pharmacist will maintain accurate records for all study drugs received and dispensed at the study site. Descriptions for the storage, preparation, handling, and administration of study drugs are presented in Sections 5.11 and 5.12.

5.11. Study Drug Storage

Study drug must be kept in a secure area. Unopened vials of RC-P should be stored at 36°F to 46°F (2°C to 8°C) and protected from light.

5.12. Study Drug Preparation/Administration

RC-P is a liquid in a sterile vial containing 10 mg of recombinant crisantaspase in 0.5 mL that should be used as supplied (refer to Study Pharmacy Manual for details of preparation). The drug product should be equilibrated to room temperature before use.

For IM administration, limit the volume of RC-P to 2 mL at a single injection site. For IV administration, slowly inject the RC-P solution into an IV infusion bag containing 100 mL of 0.9% Sodium Chloride Injection, USP (acclimatized to room temperature). Refer to the Study Pharmacy Manual and RC-P IB for details of preparation.

5.13. Study Drug Accountability, Handling, and Disposal

The Investigator or designated pharmacist will maintain accurate records of receipt of all study drugs, including dates of receipt. Study drug supplies must be kept in a secure area and dispensed

through an IRT system. Unused (or partially used) supplies must be accounted for on the drug inventory record. The receipt and dispensing of all study drugs must be documented throughout the study and reconciled at study completion.

After review of study drug accountability logs at study completion, one copy of the drug inventory record will be retained by the clinical site and the other inventory record will be retained by the Jazz Pharmaceuticals in the Trial Master File. Written documentation is mandatory. All vial labels, unused study drug, partially used study drug and empty vials will be destroyed according to site procedures and all applicable country and local regulations. The Investigator must provide a written explanation for any discrepancies in investigational product accountability.

6. STUDY PROCEDURES AND ASSESSMENTS

Study procedures and their timing are summarized in the Schedule of Assessment (Appendix 1). Protocol waivers or exemptions are not allowed.

6.1. Informed Consent and Screening

All patients of legal age will provide written informed consent that meets the requirements of the local regulations, International Council for Harmonisation (ICH) guidelines, and the Institutional Review Board (IRB)/Research Ethics Board (REB)/Independent Ethics Committee (IEC) of the study center prior to the performance of any study-related procedures (Section 10.4). Patients who are not of legal age will provide age-appropriate written or oral assent according to institutional guidelines, and their parent(s) or guardian(s) will provide written informed consent in accordance with local IRB/REB/IEC requirements before the performance of any study-related procedures. The Investigator must retain a copy of the signed informed consent form (ICF) as part of the study records and the patient will be given a copy of their signed ICF. The patient's medical record will include a statement that written informed consent and the patient's assent (if applicable) were obtained before the patient was enrolled in the study and the date written consent and patient's assent (if applicable) were obtained.

When the patient has completed the study, the signed ICF and patient's assent (if applicable) will be kept in the Investigator's study file. Regulatory authorities may check the existence of the signed ICF and documentation of a patient's assent (if applicable) in this central study folder.

All patients who enter Screening for the study (defined as the point at which the patient signs the IRB/REB/IEC approved assent/consent and, as applicable, the parent/guardian signs the IRB/REB/IEC approved consent) will receive a patient number before any study procedures are performed.

Prior to enrollment, the principal Investigator or designee will review relevant clinical documentation to ensure the patient is eligible for this trial (as defined in Section 4). Procedures that are part of standard of care will not be considered study-specific procedures. Specifically, results from standard of care procedures performed prior to signing of informed consent may be used for screening a patient as long as the procedure is performed within the timeframes specified in Appendix 1, and results are received prior to study enrollment. Laboratory tests used to document eligibility during Screening will be analyzed by an accredited laboratory.

Patients who do not meet eligibility criteria within the 28-day Screening period will not be eligible for enrollment. Patients may be re-screened at the discretion of the Investigator. If the patient is being re-screened, the patient may need to re-consent (including patient's re-assent if applicable) to the study to ensure that the valid signed informed consent has been signed within 28 days before planned enrollment. Patients who will not be re-screened or are determined ineligible after re-screen, must be considered as screen-failures.

A patient is considered enrolled within the study when they have met all eligibility criteria and enrollment confirmation has been provided in the IRT system.

6.2. Demographics/Medical History

Demographic information will be collected and recorded at Screening as permitted by regional or national regulations and should include the date that the patient (or guardian as applicable) signed the ICF, patient's age (as indicated by date of birth), sex, ethnicity, and race.

A complete medical history will be taken during Screening and should be reviewed for completeness prior to enrollment. Medical History review is required to ensure the patient is still eligible for enrollment and should ensure that all medical conditions, surgeries or procedures that occurred before the patient signed ICF are documented. Conditions that occur after the patient has signed ICF will be recorded as AEs (Section 6.7.6).

6.3. Eligibility Confirmation/Enrollment

A patient is considered enrolled within the study when they have met all eligibility criteria and enrollment confirmation has been provided in the IRT system. The Sponsor or its designee will notify study centers conducting this study when enrollment to each cohort level is open and when it closes.

6.4. Pharmacokinetic Assessments

Pharmacokinetic assessment will be based on SAA. As described in Section 6.7.4.2.1, blood samples for SAA will be collected from all patients (IM and IV patients) at pre-specified time points (Appendix 2) and will be assayed using a validated method at a Sponsor designated laboratory (as specified in the Laboratory Manual).

6.5. Immunogenicity Assessments

Immunogenicity samples will be collected at pre-specified time points as shown in Appendix 2 from all patients (IM and IV patients) and will be assayed using validated methods.

Additional samples to test for ADA (anti-RC-P antibodies) may be obtained if a patient experiences an allergic reaction. If it is determined that a patient has sub-therapeutic NSAA levels (< 0.1 IU/mL), a test for ADA may be performed if there is a blood sample available. In addition, for patients who exhibit positive ADA from samples obtained prior to the end of study (30 days after a patient's final RC-P course), efforts will be made to collect follow-up ADA samples up to approximately 6 months after a patient's last dose of their last course of RC-P. If all required assessments are completed and there is serum remaining from any of the sample types, additional immunogenicity testing may be performed.

The immunogenicity analyses will be performed by validated bioanalytical methods at a Sponsor designated laboratory (as specified in the Laboratory Manual).

6.6. Additional Assessments

Additional assessments will include the measurement of serum asparaginase concentrations (PK content). As described in Section 6.7.4.2.1, blood samples for serum asparaginase concentrations (PK content) will be collected from all patients (IM and IV patients) at pre-specified time points (Appendix 2) and will be assayed using a validated method at a Sponsor designated laboratory (as specified in the Laboratory Manual).

Additional assessments will also include the measurement of L-asparagine and L-glutamine levels (pre-specified time points as shown in Appendix 2) to assess the pharmacodynamic (PD) effect of RC-P. These levels will be assayed using validated methods at a Sponsor designated laboratory (as specified in the Laboratory Manual).

6.7. Safety Assessments

Safety will be assessed through monitoring of vital signs, physical examinations, clinical laboratory tests, and AEs as described below with the timing presented in Appendix 1.

6.7.1. Vital Signs

Vital signs (systolic and diastolic blood pressure, pulse rate) and body temperature should be measured prior to dosing after the patient has been resting for 5 minutes in a supine position as described in Appendix 1; respiratory rate is not required per protocol but may be collected if it is a standard of care at the study center. These vital signs are to be recorded. Additional monitoring of vital signs should be per institutional standard of care.

Note: When vital sign measurements and PK/PD blood samplings are scheduled for the same time point, PK/PD samples will be taken at the protocol-specified time point for IM patients or for IV patients (Appendix 2) and vital signs will be obtained before the protocol-specified PK/PD time point.

6.7.2. Physical Examination

Physical examinations are to be completed by a physician or other health professional licensed to perform such examinations. Findings will be documented. A complete physical examination, including a description of review of systems, external signs of any relevant disease, and co-morbidities should be performed at Screening, prior to the first dose of the first course of RC-P, and as specified in Appendix 1.

Height and weight will be measured at Screening for all patients and at the beginning of each course of RC-P as described in Appendix 1.

6.7.3. Laboratory Assessments

Clinical laboratory tests to be performed are listed in Table 3 and with the timing specified in Appendix 1. Samples for hematology, chemistry, coagulation, and pregnancy will be tested at an accredited local laboratory.

Any laboratory parameter that is out of range will be evaluated by the Investigator during the conduct of the study.

Calculation of estimated creatinine clearance rate will be done by the Sponsor using the appropriate formula below:

Calculation of the estimated creatinine clearance rate for patients ≥ 12 years of age will use the Cockcroft-Gault equation (FDA Guidance for Industry 2014):

$$\text{CrCl (mL/min)} = \frac{[140 - \text{age (years)}] \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}} \{\times 0.85 \text{ if female}\}$$

Calculation of the estimated creatinine clearance rate for patients < 12 years of age will use the modified Schwartz equation (FDA Guidance for Industry 2014):

CrCl (ml/min/1.73 m^2) = (K x Ht) / Scr;

height (HT) in cm, serum creatinine (Scr) in mg/dl, and K = proportionality constant

Infant (low birth weight < 1 year): K = 0.33

Infant (full term < 1 year): K = 0.45

Female child (< 12 years): K = 0.55

Male child (< 12 years): K = 0.70

Table 3: List of Laboratory Tests

Hematology (CBC): – Hemoglobin – Hematocrit – Platelets – WBC with Differential Neutrophils (Segs/Bands) Lymphocytes Monocytes Eosinophils Basophils – Blasts	Serum Chemistry: – Albumin – Alkaline Phosphatase – ALT – Amylase – AST – Calcium – Chloride – Creatinine – Glucose – Lipase – Phosphorus – Potassium – Sodium – Total bilirubin – Direct bilirubin – Total cholesterol (fasting) – Triglycerides (fasting)
Coagulation: – Prothrombin time (PT) – Activated partial thromboplastin time (aPTT) – Antithrombin III (ATIII) Activity and Antigen – Fibrinogen (Fg)	Urine pregnancy test (females of child-bearing potential only)

Abbreviations not identified in table: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CBC = complete blood count; Segs = segments.

Any laboratory parameter that is out of range and considered clinically significant (as determined by the Investigator) at the end of treatment of RC-P (last dose of the last course) must be re-evaluated.

6.7.3.1. Serum Chemistry and Hematology

Blood samples for clinical laboratory tests (serum chemistry and complete blood count [CBC], see Table 3 for details) will be collected at Screening (for serum chemistry only [lipid panel and CBC are not required at Screening]), prior to the first dose in each course, and at the end of the treatment follow-up visit 30 days after the last dose of the last course of RC-P. Any Screening laboratory tests performed within 7 days of check in on Day -1 need not be repeated on Day -1.

6.7.3.2. Coagulation Testing

Blood samples for coagulation testing (see Table 3 for details) will be collected at Day 1 of Course 1 (with a window of 7 days prior to Dose 1) and at any time the patient experiences signs or symptoms of coagulopathy/bleeding until resolution.

6.7.3.3. Pregnancy Screen

Urine samples for pregnancy testing will be collected from female patients of child-bearing potential (ie, fertile/following menarche; see full definition in List of Abbreviation and Definitions of Terms) at Screening, prior to the first dose in each course, and at the end of the study (safety follow-up 30 days after last study drug dose) as shown in Appendix 1. Patients with a positive pregnancy test will not be eligible to receive study drug.

6.7.4. Sample Collection, Storage, and Shipping

6.7.4.1. Clinical Laboratory Test Samples

Clinical safety labs will be run locally by the laboratory used by the clinical site and analyzed according to standardized, validated assays. The laboratory will supply detailed instructions and all containers for blood and urine investigations. Blood and urine sample volumes will meet the laboratory's specifications.

6.7.4.2. Bioanalytical Blood Samples

A Laboratory Manual will be provided to the site with detailed information on the collection, storage, and shipping of blood samples for PK, PD, and immunogenicity determinations. If all required assessments are completed and there is serum remaining from any of the sample types, additional immunogenicity testing may be performed.

6.7.4.2.1. Pharmacokinetic Blood Sample Collection

Blood samples (approximately 1.5 mL per time point) for PK (SAA and asparaginase content) will be collected from all patients (IM and IV patients) at pre-specified time points and will be assayed using validated methods.

The details of the blood sampling schedule and permitted time windows are provided in Appendix 2 for IM RC-P and for IV RC-P. The sampling schedule for IM and IV RC-P drug administration is the same except that the 2.5 hour postdose sample is only collected for IM administration; however, for IV administration, an end of infusion sample is collected at approximately 2 hours post the start of infusion. RC-P must be administered at a different site than the one which will be used for drawing subsequent blood samples. For those patients with a

central venous catheter, IV RC-P may be administered via peripheral IV and blood samples will be drawn via a central line.

6.7.4.2.2. Pharmacodynamic Blood Sample Collection

Blood samples (approximately 0.5 mL per time point) to assess the PD effect in patients (L-asparagine and L-glutamine levels) will be collected from all patients (IM and IV patients]) at pre-specified time points and will be assayed using validated methods.

The details of the PD blood sampling schedule and permitted time windows are provided in Appendix 2 for IM RC-P and for IV RC-P. RC-P must be administered at a different site than the one which will be used for drawing subsequent blood samples. For those patients with a central venous catheter, IV RC-P may be administered via peripheral IV and blood samples will be drawn via a central line.

6.7.4.2.3. Immunogenicity Blood Sample Collection

Blood samples (approximately 2 mL per time point) to assess immunogenicity in patients will be collected from all patients (IM and IV patients]) at pre-specified time points and will be assayed using validated methods.

The details of the immunogenicity blood sampling schedule and permitted time windows are provided in Appendix 2. RC-P must be administered at a different site than the one which will be used for drawing subsequent blood samples. For those patients with a central venous catheter, IV RC-P may be administered via peripheral IV and blood samples will be drawn via a central line.

Additional samples to test for ADA may be obtained if a patient experiences an allergic reaction. If it is determined that a patient has sub-therapeutic NSAA levels (< 0.1 IU/mL), a test for ADA may be performed if there is a blood sample available. In addition, for patients who exhibit positive ADA from samples obtained prior to the end of study (30 days after a patient's final RC-P course), efforts will be made to collect follow-up ADA samples up to approximately 6 months after a patient's last dose of their last course of RC-P. For these ADA positive patients, their follow-up ADA samples will be their End of Study samples. If all required assessments are completed and there is serum remaining from any of the sample types, additional immunogenicity testing may be performed.

6.7.5. Estimated Total Blood Volume to be Collected

The amount of blood volume collected from each patient during the study will vary depending on the number of courses of RC-P received. An overall table of estimated blood sampling volumes is provided (Table 4).

Table 4: Estimated Blood Volume

Samples	**Screening**[a]	**Course 1 Treatment Period**[b]	**Additional Course Treatment Period**[c]	**End of Study (30 days after last dose of last RC-P course)**	**Total Blood Volume per Patient if only 1 Course**
Est. Blood Volume mL (mL x number of samples)					
Comprehensive Metabolic Panel	1.0 (1.0 x 1)	1.0 (1.0 x 1)	1.0 (1.0 x 1)	1.0 (1.0 x 1)	3.0
CBC with Differential		0.5 (0.5 x 1)	0.5 (0.5 x 1)-	0.5 (0.5 x 1)-	1.0
Coagulation Panel	-	1.8 (1.8 x 1)	-	-	1.8
Lipid Panel		0.4 (0.4 x 1)-	0.4 (0.4 x 1)	0.4 (0.4 x 1)	0.8
PK (SAA and Content Assays)	-	12.0 (1.5 x 8)	4.5 (1.5 x 3)	1.5 [e] (1.5 x 1)	13.5
PD (L-Asp & L-Glu)	-	4.0 (0.5 x 8)	1.5 (0.5 x 3)	0.5 (0.5 x 1)	4.5
Immunogenicity	-	4.0 (2.0 x 2)	2.0 (1.0 x 2)	2.0 (1.0 x 2)	6.0
Approximate total blood volume per patient	1.0	23.7 [d]	9.9	5.9	30.6

[a] If Screening labs were performed within 7 days of Day-1 (Baseline), then the Screening labs do not need to be repeated at the Day -1 (Baseline) check-in.

[b] Course 1 = two week treatment period with 6 doses

[c] Additional courses (if required) are two weeks each with 6 doses; these values are not included in the overall total (last column) for Course 1.

[d] A portion of these draws (Chem, CBC, lipid, and coagulation) may be drawn up to 7 days before Dose 1

[e] PK draw at End of Study is only after a patient's last course

Notes: these approximate volumes correspond to the Parts A and B Cohort 1 patients and are the maximum volumes that will be required in this study. Reduced samples (and therefore less total volumes) will be required in Part A Cohort 2 patients. This table does not include possible additional samples (eg, additional ADA samples deemed necessary for patients with allergic reactions, sub-therapeutic NSAA levels, or positive ADA results).

If an indwelling catheter is used to draw the PK/PD samples, approximately 0.5 mL of saline diluted blood will need to be discarded prior to obtaining a non-diluted blood specimen for analysis.

Abbreviations: ADA = anti-RC-P antibodies; CBC = complete blood count; L-Asp = L-asparagine; L-Glu = L-glutamine; PD = pharmacodynamic; PK = pharmacokinetic; SAA = serum asparaginase activity

6.7.6. Adverse Event Assessment and Reporting

6.7.6.1. Adverse Events (AEs)

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered related to study drug.

Adverse events include, but are not limited to: (1) any new medical occurrence or a worsening or change in nature, severity, or frequency of conditions present at the start of the study (once informed consent is signed); (2) patient deterioration due to primary illness; (3) intercurrent illness; (4) drug interaction; and/or (5) clinically significant adverse changes from baseline routine laboratory tests (as assessed by the study Investigator), vital signs, and physical examinations.

All AEs, whether observed by the Investigator, reported by the patient, determined from laboratory findings, or other means, will be recorded (Section 6.7.6.5).

Patients should be questioned in a general way, without asking about the occurrence of any specific symptom. In general, when recording the AE, the event terminology should accurately represent the event experienced (ie, what the patient reports or what was observed); however, the Investigator should attempt to establish a diagnosis of the event (including syndromes) based on signs, symptoms, and/or other clinical information. When a diagnosis or syndrome is established, the diagnosis or syndrome and not the individual signs/symptoms should be recorded as the AE.

Following questioning and evaluation, all AEs, whether believed by the Investigator to be related or unrelated to the study drug, must be recorded in the patient's medical records, in accordance with the Investigator's normal clinical practice. Each AE is to be evaluated for duration, severity (Section 6.7.6.2), seriousness (Section 6.7.6.3), and causal relationship to the study drug (see Section 6.7.6.4).

6.7.6.2. Severity Assessment

Adverse events will be classified by the Investigator using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov). If the CTCAE grade is not specified for a particular event or if the event term does not appear in the CTCAE, general guidelines for grading severity of AEs are provided in Table 5. When the severity of an AE increases over time, the increase in the severity will be recorded as a new AE and the original AE will stop when the new AE starts except in the following scenario.

Cohort 1 (Part A and Part B): From the time written informed consent is obtained through completion of Course 1, when the severity of an AE changes over time, the decreases and increases in severity will be recorded as a new AE, and the original AE will stop when the new AE starts.

The CTCAE should be used for severity assessment only; it is not intended for use in event term selection (see Section 6.7.6.1 for AE terminology).

Table 5: CTCAE Severity Grades General Guidelines v5.0

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)[a].
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[b].
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

[a] Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Note: A semi-colon indicates 'or' within the description of the grade.

Abbreviations: ADL=activities of daily living; AE=adverse event; CTCAE=Common Terminology Criteria for Adverse Events.

Source: CTCAE v5.0 accessed at: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdfhttps://ctep.cancer.gov/.../electronic.../docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

6.7.6.3. Serious Adverse Events (SAEs)

An SAE is an AE that fulfills any of the following criteria, as per International Council on Harmonisation (ICH) E2A.II.B:

- Is fatal (results in death).
- Is life-threatening (Note: The term "life-threatening" refers to an event in which the patient was at immediate risk of death at the time of the event; it does not refer to an event that could hypothetically have caused death had it been more severe. Grade 4 laboratory values are not necessarily serious unless the patient was at immediate risk of death.).
- Requires inpatient hospitalization or prolongs existing hospitalization.
- Results in persistent or significant incapacity or disability, defined as substantial disruption of the ability to conduct normal life functions.
- Results in a congenital anomaly/birth defect.
- Is an important medical event.
  - Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above in the definition of an SAE.

- Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, the development of drug dependency or drug abuse.
- Additionally, any suspected transmission of an infectious agent via a medicinal product is considered an important medical event.

An AE should be recorded as an SAE when it meets at least one of the criteria for seriousness. A patient's underlying disease that results in the initial hospitalization is not considered an SAE. The following reasons for hospitalization are also NOT considered SAEs:

- Procedures that were planned prior to the patient entering the study.
- Social reasons and respite care in the absence of any deterioration in the patient's general condition.
- Procedures that are elective in nature and not related to worsening of an underlying condition.

Complications that occur during hospitalizations are AEs. If a complication prolongs the hospitalization, it is an SAE.

"Inpatient hospitalization" means the patient has been formally admitted to a hospital for medical reasons, for any length of time. Emergency room care without admission to a hospital is considered outpatient care.

6.7.6.4. Causal Relationship to Study Drug

The Investigator's assessment of the relationship of the AE to study drug (ie, RC-P) is required. The relationship or association of the study drug in causing or contributing to the AE will be characterized using the following classification and criteria:

Related to Study Drug	***There is a reasonable possibility that the study drug caused the event—ie, there is evidence to suggest a causal relationship between the study drug and the AE.*** Some temporal relationship exists between the event and the administration of the study drug and the event is unlikely to be explained by the patient's medical condition, other therapies, or accident. The event follows a reasonable temporal sequence from administration of the study drug and at least 1 of the following instances of clinical evidence: • The event follows a known or suspected response pattern to the study drug. • The event improves upon stopping the study drug or decreasing the dose (positive dechallenge). • The event reappears upon repeated exposure, if medically appropriate (positive rechallenge).

Not Related to Study Drug	***There is not a reasonable possibility or clinical evidence that the study drug caused the event.*** The event can be readily explained by other factors such as the patient's underlying medical conditions, concomitant therapy, or accident; or there is no temporal relationship between study drug and the event.

6.7.6.5. Adverse Event Recording and Reporting

The Investigator must record all AEs that occur from the time written informed consent is obtained until 30 days after the patient's last dose of the last course of RC-P, regardless of their relationship to study drug.

In addition, any 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, must be reported as described below.

Serious AEs must be reported to the Sponsor or its designee using an SAE Reporting Form within 24 hours of first knowledge of the event by study site personnel. The reporting form and contact information for submission of the form, will be provided to the study sites separately.

The reporting form must be completed as thoroughly as possible before transmittal to the contact provided on the form. The Investigator must provide his/her assessment of causality to the study drug and study procedure at the time of an initial SAE report. If the Investigator's assessment of causality changes after the initial report, it must be provided as follow-up information to the Sponsor.

Other Reportable Experiences:

Overdose, (defined as any dose administered or received that was higher than the intended dose), medication errors (defined as any unintentional error in the dispensing or administration of the study drug), and misuse of the study drug are considered reportable experiences and should be reported by study site personnel on an Other Reportable Experience Form. The form, and contact information for submission of the form, will be provided to the study sites separately.

If any overdose, medication error or misuse of the study drug results in an AE this must be recorded, and if this AE is serious it must also be reported as described above.

6.7.6.6. Follow-up of Adverse Events

All AEs and SAEs assessed as not related to study drug, including clinically significant laboratory tests, or physical examination findings, must be followed until the event resolves, the condition stabilizes, the event is otherwise explained, or the final study visit occurs, whichever comes first.

Adverse events and SAEs assessed as related to study drug, and AEs and SAEs resulting in discontinuation of study drug or study termination should be followed for as long as necessary to adequately evaluate the patient's safety, or until the event stabilizes, or the patient is lost to follow up. If the event resolves during the study, a resolution date should be recorded, for both AEs and SAEs. If at the time of the final scheduled study visit, the AE is not resolved, the

outcome at that time should be recorded. Once the final outcome is determined for an SAE this information should be provided as follow-up SAE information.

The Investigator is responsible for ensuring that follow-up includes any supplemental investigations indicated to elucidate the nature and/or causality of the event. This may include additional clinical laboratory testing or investigations, examinations, histopathological examinations, or consultation with other health care professionals as is practical, according to Jazz Pharmaceuticals' requests.

The Investigator should provide follow-up SAE information for any updates to information previously provided to Jazz Pharmaceuticals.

6.7.7. Reproductive Risk/Pregnancy

As stated in the study inclusion criteria (Section 4.1), female patients of childbearing potential enrolled in this study must agree to use a medically acceptable method of contraception (Section 4.3) from Screening, throughout the entire study period, and for 30 days after the patient's last dose of the last course of RC-P. Medically acceptable methods of contraception that may be used by the male partner of a female patient are condom and spermicide (or adequate and approved alternatives) or vasectomy (> 6 months prior to Day -1). Male patients enrolled in this study agree to refrain from sperm donation for 30 days after the patient completes the study and to use adequate contraception (as described above) throughout the entire study period and for 30 days after the patient's last dose of the last course of RC-P.

If a patient or a male patient's partner becomes pregnant any time after study drug dosing until 30 days after study drug dosing, the pregnancy must be reported within 24 hours of first knowledge of the event by study site personnel. RC-P must be stopped for any pregnant subject (see Section 6.8.1). The Pregnancy Reporting Form should be used to report the pregnancy. The pregnancy of a patient or a male patient's partner (once informed consent is signed) must be followed until the outcome of the pregnancy is known, and in the case of a live birth, for 6 months following the birth of the child. The Infant Follow-up Form should be used to report information regarding the status of the infant.

The Pregnancy Report Form, Infant Follow-up Form, and contact information for submission of the form, will be provided to the study sites separately.

6.7.8. Regulatory Reporting

Jazz Pharmaceuticals or its designee is responsible for reporting relevant SAEs to the relevant regulatory authorities, concerned Central Ethics Committees (CECs) and participating Investigators, in accordance with ICH guidelines, the US Code of Federal Regulations (CFR), the EU Clinical Trial Directive (2001/20/EC) and/or local regulatory requirements.

The reference safety information to determine expectedness of RC-P treatment-emergent SAEs is specified in the RC-P IB.

Suspected unexpected serious adverse reactions (SUSARs) will be reported to the relevant regulatory authorities, CECs, and participating Investigators no later than 15 days after first knowledge of the event.

SUSARs that are fatal or life-threatening will be reported to the relevant regulatory authorities and CECs no later than 7 days after knowledge of such a case, and relevant follow-up information provided within an additional 8 days.

Once a year throughout the clinical study, a report listing of all SUSARs (and SAEs if required by local regulation) that have occurred during this period and a report of the patient's safety will be submitted to the applicable authorities, and as otherwise required by local laws.

Reporting of SAEs by the Investigator to his/her local ethics committee will be done in accordance with the standard operating procedures and policies of the ethics committee. Adequate documentation must be maintained showing that the IRB/REB/IEC was properly notified.

The events listed below will NOT be reported to FDA expeditiously as Investigational New Drug (IND) individual case safety reports unless fatal or life-threatening. These events will be reported to FDA as IND safety reports only if aggregate analysis by Jazz indicates that the event is occurring more frequently than anticipated.

Events that are commonly reported as asparaginase-related toxicities in pediatric patients (Raetz & Salzer 2010)

Allergic reaction (including hypersensitivity and anaphylactic reaction)

Pancreatitis

Thrombosis

Hyperglycemia

Events that are common in the study population

Fever (including febrile neutropenia)

Infections (including bacterial, fungal, and viral)

Hemorrhage

Nausea/Vomiting

6.8. Removal of Patients from the Study or Study Drug

6.8.1. Patient Withdrawal

Patients may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the Investigator or Jazz Pharmaceuticals or its designee at any time for any reason.

In accordance with the ICH principles of GCP, the Investigator may advise a patient to withdraw from the study if the patient's safety or well-being is compromised by his or her further participation in study. Other reasons for withdrawal may include the following:

- Patient withdraws consent
- Death

- Adverse event which in the opinion of the Investigator contraindicates continuation in the study
- Noncompliance with study drug
- Investigator considers it not in the patient's best interest to continue in the study
- Pregnancy
- Jazz Pharmaceuticals (or its designee) decision to terminate study

For all patients who prematurely discontinue the study, an attempt should be made to perform all discharge safety follow-up assessments 30 days after the last dose for the last course of RC-P. If the patient refuses to complete all of the 30-day safety follow up assessments, then as many assessments as possible should be completed; at a minimum the AE review.

The specific reason for the discontinuation should be carefully documented. If a patient withdraws informed consent, the specific reason for withdrawing the informed consent should be stated.

Adverse events resulting in discontinuation of study drug or study termination should be followed for as long as necessary to adequately evaluate the patient's safety, or until the event stabilizes, or the patient is lost to follow up. If the event resolves during the study, a resolution date should be recorded, for both AEs and SAEs. If at the time of the final scheduled study visit, the AE resulting in discontinuation of study drug or study termination is not resolved, the outcome at that time should be recorded. Once the final outcome is determined for an SAE this information should be provided as follow-up SAE information.

To ensure sufficient numbers of evaluable patients are available with PK data, additional patients may be enrolled as necessary upon agreement of the Investigator and Sponsor.

6.8.2. Sponsor's Termination of the Study

Jazz Pharmaceuticals reserves the right to discontinue the study at any time for any reason. Such a termination must be implemented by the Investigator, if instructed to do so by Jazz Pharmaceuticals, in a time frame that is compatible with the patients' well-being.

The Sponsor may determine to discontinue an arm of the study within a cohort or a complete cohort based on the efficacy and safety/tolerability results (Section 3.1.3).

6.9. Appropriateness of Measurements

The PK blood sampling and analyses for this study are considered sufficient to characterize the SAA-time profiles. The parameters (monitoring of AEs, clinical laboratory tests, vital signs, and physical examinations) selected to assess the safety of each of these study drugs are appropriate since they are routinely used to assess the safety profile of drugs in clinical studies.

7. STUDY ACTIVITIES

Study procedures and assessments are provided in Section 6 with the timing presented in Appendix 1; the PK and PD sampling schedule for IM RC-P and IV RC-P patients is in Appendix 2.

8. PLANNED STATISTICAL ANALYSIS

8.1. General Considerations

Data from the study will be summarized by dose level for both IM RC-P (Part A) and IV RC-P (Part B) patients in general. Categorical variables (eg, sex, race, etc.) will be reported using frequency and percentage. Continuous variables (eg, age, weight, etc.) will be reported using the number of patients (n), mean, standard deviation, median, minimum, and maximum. All summaries, statistical analyses, and individual patient data listings described below will be completed using Version 9.4 or later of the Statistical Analysis System (SAS Institute, Inc. Cary, NC).

8.2. Treatment Assignments

Patients in Part A will be allocated IM RC-P and patients in Part B will be allocated IV RC-P as described in Section 5.6.

8.3. Determination of Sample Size

For Part A (RC-P by IM administration, Cohorts 1 and 2) 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 ≥ 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 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 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.

The probability of the lower bound of the 95% CI exceeds 90% will be less than 80% with a sample size of 98 patients if the true response rate is less than 96%. For example, if the true response rate is 94% for the primary efficacy endpoint, with a 5% drop out rate, a sample size of 98 patients provides 51% probability that the lower bound of the 95% CI exceeds 90%.

For Part B (RC-P by IV administration, Cohort 1), 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.

8.4. Analysis Sets and Handling of Dropouts

- Enrolled Analysis Set will include patients who signed the informed consent and meet inclusion/exclusion criteria per Investigator
- Safety Analysis Set will include patients who received at least one dose of RC-P
- Efficacy Analysis Set will include patients who received at least one dose of RC-P and have at least one 48- or 72-hour NSAA assessment collected within the protocol-defined sample collection window (± 2 hours) in Course 1
- PK Analysis Set will include patients who received at least one dose of RC-P and have at least one postdose evaluable SAA or PK concentration value
- PD Analysis Set will include patients who received at least one dose of RC-P and have at least one postdose evaluable L-asparagine or L-glutamine value

8.5. Handling of Missing Data

In general, missing data will be treated as missing completely at random and will not be imputed. Handling of missing PK concentrations and PK concentrations that are below the limit of quantitation (BLQ) will be described in the statistical analysis plan (SAP).

8.6. Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized using descriptive statistics for the Efficacy, Safety, and PK Analysis Sets by dose level of RC-P and route of administration (IM or IV).

Medical history will be listed. Prior medications and concomitant medications will be summarized.

8.7. Efficacy Analyses

8.7.1. Primary Efficacy Endpoint and Analysis

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.

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 (confidence interval) will be provided. The primary efficacy endpoint will be met if the lower bound of the 95% CI of the response rate exceeds 90%.

8.7.2. Secondary Efficacy Endpoints and Analyses

Secondary efficacy endpoints include the following from Part A of the study:

- Key secondary efficacy 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
- Proportion of patients with the last 48-hour 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

8.7.2.1. Key Secondary Efficacy 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

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 will be analyzed using the same methodology as the primary efficacy endpoint 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 response rate, along with the 95% Wald CI will be provided.

8.7.2.2. 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. This analysis will use the same methodology as the primary efficacy endpoint 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 response rate, along with the 95% Wald CI will be provided.

8.7.2.3. 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. This analysis will use the same methodology as the primary efficacy endpoint 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 response rate, along with the 95% Wald CI will be provided.

8.7.3. Exploratory Efficacy Endpoints and Analyses

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

- 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

8.7.3.1. 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. This analysis will use similar methodology as the primary efficacy endpoint using the Efficacy Analysis Set for patients administered the final IV RC-P dose level in Part B with at least one 48-hour NSAA assessment collected within the protocol-defined sample collection window (± 2 hours) in Course 1. The response rate, along with the 95% CI will be provided.

8.7.3.2. 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. This analysis will use similar methodology as the primary efficacy endpoint using the Efficacy Analysis Set for patients administered the final IV RC-P dose level in Part B with at least one 72-hour NSAA assessment collected within the protocol-defined sample collection window (± 2 hours) in Course 1. The response rate, along with the 95% CI will be provided.

8.7.3.3. 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. This analysis will use similar methodology as the primary efficacy endpoint using the Efficacy Analysis Set for patients administered the final IV RC-P dose level in Part B with at least one 48-hour NSAA assessment collected within the protocol-defined sample collection window (± 2 hours) in Course 1. The response rate, along with the 95% CI will be provided.

8.7.3.4. 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. This analysis will use similar methodology as the primary efficacy endpoint using the Efficacy Analysis Set for patients administered the final IV RC-P dose level in Part B with at least one 72-hour NSAA assessment collected within the protocol-defined sample collection window (± 2 hours) in Course 1. The response rate, along with the 95% CI will be provided

8.8. Pharmacokinetic, Pharmacodynamic, and Immunogenicity Analyses

Individual RC-P PK (SAA and serum asparaginase concentration levels) and PD (asparagine and glutamine concentrations) measurements will be listed by time, cohort (dose level), and route of administration (IM or IV). Descriptive statistics including number of patients, mean, standard deviation (SD), minimum, median, maximum, coefficient of variation (CV), geometric mean, and geometric standard deviation will be used to summarize PK and PD data by time, cohort (dose level), and route of administration (IM or IV), as appropriate. Immunogenicity results will be listed as positive or negative for the presence of anti-RC-P antibodies for each patient by cohort (dose level) and route of administration (IM or IV). Number and percentage of anti-RC-P antibody positive results will be provided. Individual and/or summary figures of SAA-time or enzyme content-time profiles in serum may be provided on semi-log and linear scales. Individual and/or summary figures of SAA versus PD profiles may also be provided. For those patients with results from alternate immunogenicity assays, the presence of anti-asparaginase antibodies at baseline based on the assay used will also be reported.

Statistical summaries and displays will be based on scheduled sampling times unless significant deviations (outside of the specified time windows in Appendix 2) of actual sampling times from scheduled sampling times occur. 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 clinical study report in a standalone document.

8.9. Safety Analysis

The safety and tolerability evaluations of IM RC-P in patients with ALL/LBL who are hypersensitive to *E. coli*-derived asparaginases will be assessed by the occurrence of treatment-emergent adverse events (TEAEs) for the Safety Analysis Set.

The incidence of TEAEs for the Safety Analysis Set will be summarized by dose level in Part A and Part B. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) to classify events under primary system organ class and preferred term. In addition, TEAEs, serious TEAEs, TEAEs leading to discontinuation of study drug, CTCAE Grade 3 or above TEAEs, TEAEs related to study drug, and deaths (if any) will be summarized and/or listed as appropriate.

Descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) as well as changes from Baseline (ie, the latest non-missing value obtained prior to or at the start date and/or time of the first dose of IM RC-P) will be presented by dose level in Part A and Part B for vital signs and clinical laboratory results.

No formal statistical testing will be performed for the safety analyses.

9. DATA QUALITY ASSURANCE AND QUALITY CONTROL

Steps to assure the accuracy and reliability of data include the selection of qualified Investigators and appropriate study sites, review of protocol procedures with the Investigator and associated personnel prior to the study, and periodic monitoring visits by Jazz Pharmaceuticals or its designee. Data are reviewed throughout the study through programmed checks, reports, and manual review. Any discrepancies will be resolved with the Investigator or designees as appropriate.

9.1. Quality Assurance

This study will be conducted according to GCP Guidelines and according to local and national law. Quality assurance audits may be performed at the discretion of Jazz Pharmaceuticals.

9.2. Clinical Data Management

The standard procedures for handling and processing records will be followed in compliance with 21 CFR Part 11, FDA and ICH Regulations and Guidelines, GCPs, and the Standard Operating Procedures (SOPs) of Jazz Pharmaceuticals and/or the contract research organization (CRO). A comprehensive Data Management Plan (DMP) will be developed to document data sources, systems, and handling.

9.3. Electronic Case Report Forms (eCRFs)

All patient data required by the protocol to be reported to Jazz Pharmaceuticals (Sponsor) on each study patient will be recorded by clinical site staff in eCRFs developed by the Sponsor or its designee, unless such data are transmitted to the Sponsor or designee electronically (eg, central laboratory data, data from an IRT system, eCOA [electronic Clinical Outcome Assessment] data, etc.). Electronic data sources will be identified in the DMP. The Principal Investigator must review the eCRFs and provide his/her signature certifying that he/she has reviewed the eCRF data and considers the eCRFs complete and accurate to the best of his/her knowledge. Regardless of who signs or completes the forms, it is the Principal Investigator's responsibility to ensure their completeness and accuracy.

9.4. Retention of Data

The Investigator/institution should maintain the study documents as specified in Essential Documents for the Conduct of a Trial (ICH E6 Good Clinical Practice) and as required by the applicable regulatory requirement(s). The Investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of Jazz Pharmaceuticals to inform the Investigator/institution when these documents no longer need to be retained.

9.5. Data Safety Monitoring

The Sponsor recognizes the importance of ongoing review of the accumulating safety data and will perform periodic data monitoring regularly by data listing review. In addition, safety data from the study will be reviewed on an ongoing basis as part of routine pharmacovigilance and safety surveillance activities. An internal product-specific cross-functional Safety Management Team will also be perform a systematic evaluation of all relevant emerging safety information from the study. Reports of safety findings (from either single events or based on aggregate review) that suggest a significant risk to humans will be distributed to all participating Investigators and to the relevant regulatory authorities and IRBs/REBs/IECs.

Decisions pertaining to the safety and tolerability evaluations by an SDRC as described below in Section 9.6 will be documented. The Sponsor believes that a Data and Safety Monitoring Board is not required for the study (single arm and open-label study design), and that this opinion is in line with the FDA guidance (Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees, March 2006).

9.6. Study Data Review Committee (SDRC)

The SDRC will include representatives from the Sponsor and the COG Study Team. The SDRC will review the NSAA levels and safety assessments including but not limited to AEs in Part A of the study for all patients at any RC-P dose level for Cohort 1 to select the dose for Cohort 2; the SDRC will continue monitoring the NSAA levels and safety assessments for Cohort 2 as well. In Part B of the study, the SDRC will also monitor NSAA levels and safety to confirm an IV dose for possible future expansion.

The general timing of the SDRC reviews throughout the study is planned as follows: for Part A at n = 6 and 13 (Cohort 1), 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.

The membership, roles and responsibilities of the SDRC, as well as the detail of the timing of NSAA levels and safety reviews, will be fully described in the SDRC Charter.

10. ADMINISTRATIVE CONSIDERATIONS

10.1. Investigators and Study Administrative Structure

Parties (eg, Sponsor, CROs, and vendors) responsible for the various functions in this study will be listed in a separate document and filed in the Trial Master File.

10.2. Institutional Review Board (IRB)/Research Ethics Board (REB)/Independent Ethics Committee (IEC)

The final approved protocol and the informed consent form will be reviewed by the IRB/REB/IEC. In addition, the IRB/REB/IEC will review any other written information to be provided to the patient, advertisements for patient recruitment (if used), and patient compensation (if any). The committee's decision concerning conduct of the study will be sent in writing to the Investigator and a copy will be forwarded to Jazz Pharmaceuticals. The Investigator agrees to make any required progress reports, as well as reports of SAEs, life threatening problems, death, or any significant protocol deviations, as required by the IRB/REB/IEC.

A list of the IRB/REB/IEC members who actually participated in the review, their respective titles (occupational identification), and institutional affiliations or an IRB/REB/IEC assurance number must be provided to Jazz Pharmaceuticals. The approval letter or notice must be provided on IRB/REB/IEC letterhead and contain the date of the meeting and sufficient information to identify the version of the protocol unambiguously (by name and number) and state that the informed consent form was also reviewed.

A clinical study may not be initiated before the proposed protocol and informed consent form have been reviewed and unconditionally approved by an IRB/REB/IEC meeting federal regulations. The clinical study remains subject to continuing review by the IRB/REB/IEC. Jazz Pharmaceuticals or its designee will supply all necessary data for the Investigator to submit to the IRB/REB/IEC. Jazz Pharmaceuticals will not ship clinical supplies to an investigational site until written signed approval from the site's IRB/REB/IEC has been received by Jazz Pharmaceuticals.

The Investigator is responsible for ensuring initial and continued review and approval of the clinical study by the IRB/REB/IEC at his/her site. The Investigator must also ensure that he/she will promptly report to the IRB/REB/IEC and Jazz Pharmaceuticals all changes in the research activity and all unanticipated problems involving risk to human patients or others, and that he/she will not make any changes in the research without IRB/REB/IEC approval, except where necessary to eliminate apparent hazards to human patients. If the study remains in progress for more than 1 year, documentation of annual renewal must be submitted to Jazz Pharmaceuticals or its designee. Within 3 months of study completion or termination, a final report must be provided to the IRB/REB/IEC by the clinical site.

10.3. Ethical/Legal Conduct of the Study

The study will be conducted in accordance with applicable local regulations relating GCP and with the SOPs of the CRO or Jazz Pharmaceuticals, as applicable. These standards respect the following guidelines or laws:

- Guideline for Good Clinical Practice E6 (R2): Consolidated Guideline (International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use, 01 December 2016).
- US Code of Federal Regulations (CFR) pertaining to conduct and reporting of clinical studies (Title 21 CFR Parts 11, 50, 54, 56, 312, and 314).
- Current Declaration of Helsinki, concerning medical research in humans ("WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Patients," Fortaleza 2013).

10.4. Patient Information and Consent

All patients of legal age will provide their written informed consent before the performance of any study related procedures. Patients who are not of legal age will provide age-appropriate written or oral assent according to institutional guidelines, and their parent(s) or guardian(s) will provide written informed consent in accordance with local IRB/REB/IEC requirements before the performance of any study-related procedures. The Investigator must provide a copy of the ICF to the study patient.

Each patient's chart will have his/her signed ICF for study participation attached to it and documentation (written or verbal) of the patient's assent (if applicable). When the patient has completed the study and the eCRF has been monitored, the ICF will be kept in the Investigator's study file. Regulatory authorities may check the existence of the signed ICF and documentation of a patient's assent (if applicable) in this central study folder if not having done so during the performance of the trial.

10.5. Patient Confidentiality

All reports and communications relating to the patients in the study will identify each patient only by the patient's study number. These documents will be treated with strict adherence to professional standards of confidentiality and will be filed at the study site under adequate security and restricted access.

Portions of the patient's medical records pertinent to the study will be reviewed by Jazz Pharmaceuticals personnel or its designee and possibly by governmental agency personnel to ensure adequate source documentation, accuracy, and completeness of the eCRFs. The IRB/REB/IEC has the authority to review patient records.

10.6. Protocol Adherence - Amendments

The Investigator must not implement any prospective deviations from the protocol. Any amendments will be agreed upon and approved in writing by the Investigator and Jazz Pharmaceuticals designees. The IRB/REB/IEC will be notified of all amendments to the protocol. Amendments to the protocol will not be implemented until written IRB/REB/IEC approval has been received.

10.7. Required Documents

The Investigator must provide Jazz Pharmaceuticals or its designee with the applicable regulatory documents before the enrollment of any patient (copies should be kept by the Investigator in the Investigator's regulatory document binder).

10.8. Study Monitoring

Throughout the course of the study, the study monitor will make frequent contacts with the Investigator. This will include, but is not limited to telephone calls and onsite visits. During the onsite visits, the eCRFs will be reviewed for completeness and adherence to the protocol. As part of the data verification, source documents will be made available for review by the site. The study monitor will also perform drug accountability checks and will periodically request review of the Investigator study file to assure completeness of documentation in all respects of clinical study conduct.

Upon completion of the study, the study monitor will arrange for a final review of the study files after which the files should be secured for the appropriate time period. The Investigator or appointed delegate will receive the study monitor during these onsite visits and will cooperate in providing the documents for review and respond to inquiries. In addition, the Investigator will permit inspection of the study files by authorized representatives of the regulatory agencies.

10.9. Protocol Deviations

All major protocol deviations must be reported to the IRB/REB/IEC per their relevant guidelines. It is the responsibility of the principal Investigator to ensure proper reporting to the IRB/REB/IEC. Protocol deviations should be reported to Jazz Pharmaceuticals or designee.

10.10. Access to Source Documentation

The Investigator/institution will permit trial-related monitoring (Section 10.8), audits conducted by the Clinical Quality Assurance Department of Jazz Pharmaceuticals or designee, ethics committee review and regulatory inspections by providing direct access to source data and documents for the study. Jazz Pharmaceuticals (or its designee) will be responsible for monitoring this study. Jazz Pharmaceuticals will monitor the study conduct, proper eCRF and source documentation completion and retention, and accurate study drug accountability. It is essential that the monitor have access to all documents (related to the study and the individual participants) at any time they are requested. In turn, the monitor will adhere to all requirements for study patient confidentiality as outlined in the informed consent form. The Investigator and his/her staff will be expected to cooperate with the monitor, to be available during a portion of the monitoring visit to answer questions, and to provide any missing information.

In addition, representatives of the Quality Assurance Department of Jazz Pharmaceuticals (or designee), or appointed monitoring organization(s), and representatives of the FDA or other regulatory agencies may request to inspect the study documents (eg, study protocol, eCRFs, study drug accountability records, and original medical records/files). All study patient data will be treated confidentially.

10.11. Data Generation and Analysis

Information regarding data management and data collection is provided in Sections 9.2 and 9.3, respectively. Information on planned data analyses is provided in Section 8.

10.12. Publication and Disclosure Policy

Please refer to individual site contracts for specific contractual obligations and requirements.

All information concerning RC-P, Jazz Pharmaceuticals' operations, patent applications, formulas, manufacturing processes, basic scientific data, and formulation information supplied by Jazz Pharmaceuticals to the Investigator and not previously published, are considered confidential and remain the sole property of Jazz Pharmaceuticals. Electronic CRFs also remain the property of Jazz Pharmaceuticals. The Investigator agrees to use this information only to complete this study and will not use it for other purposes without written consent of Jazz Pharmaceuticals as further detailed in the Clinical Study Agreement signed by the Investigator and/or institution.

It is understood by the Investigator that Jazz Pharmaceuticals will use the information obtained in this clinical study in connection with the study of RC-P, and therefore may disclose this information as required to other Jazz Pharmaceuticals Investigators; appropriate international regulatory agencies; or others. In agreeing to participate in this study, the Investigator understands that he/she has an obligation to provide complete test results and all data developed during this study to Jazz Pharmaceuticals. Jazz Pharmaceuticals requires that permission to publish details of this study must be obtained in writing as further detailed in the Clinical Study Agreement signed by the Investigator and/or institution. It is intended that the results of this study may be published in scientific literature. The conditions noted here are intended to protect commercial confidential materials (patents, etc.) and not to restrict publication.

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APPENDIX 1. SCHEDULE FOR PROCEDURES AND ASSESSMENTS

Monday Start

Assessment[a]	Screening	Course 1 and Subsequent Courses														EOS [h]
Study Day	**-28 to -1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**30 days (±3) after last dose**
Weekday		**M**	**T**	**W**	**Th**	**F**	**Sa**	**Su**	**M**	**T**	**W**	**Th**	**F**	**Sa**	**Su**	**M-F**
Informed consent	X															
Prior Medications	X															
Demographics	X															
Medical History	X															
Height	X	X[b]														
Weight	X	X[b]														
Physical Examination[c]	X	X[d]														X
Vital Signs and Temperature[c]	X	X		X		X			X		X		X			X
Local Lab Urine Pregnancy Test (Females of Child-bearing potential)	X[g]	X[e]														X
Local Lab Serum Chemistry[f]	X[g]	X														X
Local Lab Hematology (CBC)[f]		X														X

Assessment[a]	**Screening**	**Course 1 and Subsequent Courses**														**EOS**[h]
Study Day	**-28 to -1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**30 days (±3) after last dose**
Weekday		**M**	**T**	**W**	**Th**	**F**	**Sa**	**Su**	**M**	**T**	**W**	**Th**	**F**	**Sa**	**Su**	**M-F**
Local Lab Coagulation[f]		X														
RC-P Drug Administration (IM or IV)		X		X		X			X		X		X			
Pharmacokinetics	Refer to Appendix 2															
Pharmacodynamics	Refer to Appendix 2															
Immunogenicity	Refer to Appendix 2															
Adverse Event Review	X	X		X		X			X		X		X			X
Concomitant Medications Review	X	X		X		X			X		X		X			X

[a] When multiple procedures are scheduled for the same time point, PK and PD samples will be taken at the protocol assigned time point as specified in Appendix 2 and other non-PK and non-PD measurements will be taken before (ie, vital signs) or after (ie, AE review, clinical laboratory evaluation) the protocol-specified PK and PD time point. The window for PK and PD assessments is specified in Appendix 2. Unless otherwise specified, all procedures are to be completed prior to dosing with RC-P.

[b] Performed at the beginning of each course with a -3 day window.

[c] A complete physical examination, including a description of a review of systems, external signs of any relevant disease, and co-morbidities should be performed. Physical examinations are to be completed by a physician or other health professional licensed to perform such examinations. Findings will be documented in the patient's medical record and recorded. Blood pressure, pulse rate, and temperature should be measured after the patient has been resting for 5 minutes in a supine position; respiratory rate is not required per protocol but may be collected if it is a standard of care at the study center. Blood pressure (systolic and diastolic) and pulse rate will be measured at Screening, predose, and as per the institutional standard of care. Temperature is measured only at Screening, predose, and at EOS.

[d] Physical Examination can be done within 3 days prior to each course (initial and subsequent courses).

[e] If a Screening urine pregnancy test was performed within 7 days of Day 1, it need not be repeated on Day 1.

[f] Clinical laboratory tests include serum chemistry (albumin, alkaline phosphatase, ALT, amylase, AST, calcium, chloride, creatinine, glucose, lipase, phosphorus, potassium, sodium, total bilirubin, direct bilirubin, total cholesterol [fasting], and triglycerides [fasting]) and CBC with differential. Lipid panel analytes are not required at Screening. Coagulation tests are to be performed at Day 1 of Course 1 and at any time the patient is symptomatic; testing will include the following: PT, aPTT, ATIII activity and antigen, and Fg. See Table 3 for additional information. Any laboratory parameter that is out of range and considered clinically significant (as determined by the Investigator) at the end of treatment of RC-P (last dose of the last course) must be re-evaluated until resolution. Windows for the above laboratory tests: 7 days prior to Dose 1.

[g] Screening laboratory testing should be completed within 7 days of enrollment. Any Screening laboratory tests performed within 7 days of check in on Day -1 need not be repeated on Day -1.

[h] For ADA positive patients, their follow-up ADA samples will be their End of Study samples (Section 6.7.4.2.3 and Appendix 2).

Abbreviations: ADA = anti-RC-P antibodies; AE = adverse event; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; ATIII = antithrombin III activity and antigen; CBC = Complete Blood Count; EOS = end of study; Fg = fibrinogen; IM = intramuscular; IV = intravenous; PD = pharmacodynamic; PK = pharmacokinetic; PT = prothrombin time; RC-P = Recombinant Crisantaspase produced in *Pseudomonas fluorescens;* WBC = white blood cells.

Wednesday Start

Assessment[a]	Screening	Course 1 and Subsequent Courses														EOS [h]
Study Day	**-28 to -1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**30 days (±3) after last dose**
Weekday		**W**	**Th**	**F**	**Sa**	**Su**	**M**	**T**	**W**	**Th**	**F**	**Sa**	**Su**	**M**	**T**	**M-F**
Informed consent	X															
Prior Medications	X															
Demographics	X															
Medical History	X															
Height	X	X[b]														
Weight	X	X[b]														
Physical Examination[c]	X	X[d]														X
Vital Signs and Temperature[c]	X	X		X			X		X		X			X		X
Local Lab Urine Pregnancy Test (Females of Child-bearing potential)	X[g]	X[e]														X
Local Lab Serum Chemistry[f]	X[g]	X														X
Local Lab Hematology (CBC)[f]		X														X
Local Lab Coagulation[f]		X														
RC-P Drug Administration (IM or IV)		X		X			X		X		X			X		

Assessment[a]	**Screening**	**Course 1 and Subsequent Courses**														**EOS** [h]
Study Day	**-28 to -1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**30 days (±3) after last dose**
Weekday		**W**	**Th**	**F**	**Sa**	**Su**	**M**	**T**	**W**	**Th**	**F**	**Sa**	**Su**	**M**	**T**	**M-F**
Pharmacokinetics	Refer to Appendix 2															
Pharmacodynamics	Refer to Appendix 2															
Immunogenicity	Refer to Appendix 2															
Adverse Event Review	X	X		X			X		X		X			X		X
Concomitant Medications Review	X	X		X			X		X		X			X		X

[a] When multiple procedures are scheduled for the same time point, PK and PD samples will be taken at the protocol assigned time point as specified in Appendix 2 and other non-PK and non-PD measurements will be taken before (ie, vital signs) or after (ie, AE review, clinical laboratory evaluation) the protocol-specified PK and PD time point. The window for PK and PD assessments is specified in Appendix 2. Unless otherwise specified, all procedures are to be completed prior to dosing with RC-P.

[b] Performed at the beginning of each course with a -3 day window.

[c] A complete physical examination, including a description of a review of systems, external signs of any relevant disease, and co-morbidities should be performed. Physical examinations are to be completed by a physician or other health professional licensed to perform such examinations. Findings will be documented in the patient's medical record and recorded. Blood pressure, pulse rate, and temperature should be measured after the patient has been resting for 5 minutes in a supine position; respiratory rate is not required per protocol but may be collected if it is a standard of care at the study center. Blood pressure (systolic and diastolic) and pulse rate will be measured at Screening, predose, and as per the institutional standard of care. Temperature is measured only at Screening, predose, and at EOS.

[d] Physical Examination can be done within 3 days prior to each course (initial and subsequent courses).

[e] If a Screening urine pregnancy test was performed within 7 days of Day 1, it need not be repeated on Day 1.

[f] Clinical laboratory tests include serum chemistry (albumin, alkaline phosphatase, ALT, amylase, AST, calcium, chloride, creatinine, glucose, lipase, phosphorus, potassium, sodium, total bilirubin, direct bilirubin, total cholesterol [fasting], and triglycerides [fasting]) and CBC with differential. Lipid panel analytes are not required at Screening. Coagulation tests are to be performed at Day 1 of Course 1 and at any time the patient is symptomatic; testing will include the following: PT, aPTT, ATIII activity and antigen, and Fg. See Table 3 for additional information. Any laboratory parameter that is out of range and considered clinically significant (as determined by the Investigator) at the end of treatment of RC-P (last dose of the last course) must be re-evaluated until resolution. Windows for the above laboratory tests: 7 days prior to Dose 1.

[g] Screening laboratory testing should be completed within 7 days of enrollment. Any Screening laboratory tests performed within 7 days of check in on Day -1 need not be repeated on Day -1.

[h] For ADA positive patients, their follow-up ADA samples will be their End of Study samples (Section 6.7.4.2.3 and Appendix 2).

Abbreviations: ADA = anti-RC-P antibodies; AE = adverse event; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; ATIII = antithrombin III activity and antigen; CBC = Complete Blood Count; EOS = end of study; Fg = fibrinogen; IM = intramuscular; IV = intravenous; PD = pharmacodynamic; PK = pharmacokinetic; PT = prothrombin time; RC-P = Recombinant Crisantaspase produced in *Pseudomonas fluorescens;* WBC = white blood cells.

Friday Start

Assessment[a]	**Screening**	**Course 1 and Subsequent Courses**														**EOS**[h]
Study Day	**-28 to -1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**30 days (±3) after last dose**
Weekday		**F**	**Sa**	**Su**	**M**	**T**	**W**	**Th**	**F**	**Sa**	**Su**	**M**	**T**	**W**	**Th**	**M-F**
Informed consent	X															
Prior Medications	X															
Demographics	X															
Medical History	X															
Height	X	X[b]														
Weight	X	X[b]														
Physical Examination[c]	X	X[d]														X
Vital Signs and Temperature[c]	X	X			X		X		X			X		X		X
Local Urine Pregnancy Test (Females of Child-bearing potential)	X[g]	X[e]														X
Local Lab Serum Chemistry[f]	X[g]	X														X
Local Lab Hematology (CBC)[f]		X														X

Assessment[a]	**Screening**	**Course 1 and Subsequent Courses**														**EOS**[h]
Study Day	**-28 to -1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**30 days (±3) after last dose**
Weekday		**F**	**Sa**	**Su**	**M**	**T**	**W**	**Th**	**F**	**Sa**	**Su**	**M**	**T**	**W**	**Th**	**M-F**
Local Lab Coagulation[f]		X														
RC-P Administration (IM or IV)		X			X		X		X			X		X		
Pharmacokinetics	Refer to Appendix 2															
Pharmacodynamics	Refer to Appendix 2															
Immunogenicity	Refer to Appendix 2															
Adverse Event Review	X	X			X		X		X			X		X		X
Concomitant Medications Review	X	X			X		X		X			X		X		X

[a] When multiple procedures are scheduled for the same time point, PK and PD samples will be taken at the protocol assigned time point as specified in Appendix 2 and other non-PK and non-PD measurements will be taken before (ie, vital signs) or after (ie, AE review, clinical laboratory evaluation) the protocol-specified PK and PD time point. The window for PK and PD assessments is specified in Appendix 2. Unless otherwise specified, all procedures are to be completed prior to dosing with RC-P.

[b] Performed at the beginning of each course with a -3 day window.

[c] A complete physical examination, including a description of a review of systems, external signs of any relevant disease, and co-morbidities should be performed. Physical examinations are to be completed by a physician or other health professional licensed to perform such examinations. Findings will be documented in the patient's medical record and recorded. Blood pressure, pulse rate, and temperature should be measured after the patient has been resting for 5 minutes in a supine position; respiratory rate is not required per protocol but may be collected if it is a standard of care at the study center. Blood pressure (systolic and diastolic) and pulse rate will be measured at Screening, predose, and as per the institutional standard of care. Temperature is measured only at Screening, predose, and at EOS.

[d] Physical Examination can be done within 3 days prior to each course (initial and subsequent courses).

[e] If a Screening urine pregnancy test was performed within 7 days of Day 1, it need not be repeated on Day 1.

[f] Clinical laboratory tests include serum chemistry (albumin, alkaline phosphatase, ALT, amylase, AST, calcium, chloride, creatinine, glucose, lipase, phosphorus, potassium, sodium, total bilirubin, direct bilirubin, total cholesterol [fasting], and triglycerides [fasting]) and CBC with differential. Lipid panel analytes are not required at Screening.

Coagulation tests are to be performed at Day 1 of Course 1 and at any time the patient is symptomatic; testing will include the following: PT, aPTT, ATIII activity and antigen, and Fg. See Table 3 for additional information. Any laboratory parameter that is out of range and considered clinically significant (as determined by the Investigator) at the end of treatment of RC-P (last dose of the last course) must be re-evaluated until resolution. Windows for the above laboratory tests: 7 days prior to Dose 1.

[g] Screening laboratory testing should be completed within 7 days of enrollment. Any Screening laboratory tests performed within 7 days of check in on Day -1 need not be repeated on Day -1.

[h] For ADA positive patients, their follow-up ADA samples will be their End of Study samples (Section 6.7.4.2.3 and Appendix 2).

Abbreviations: ADA = anti-RC-P antibodies; AE = adverse event; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; ATIII = antithrombin III activity and antigen; CBC = Complete Blood Count; EOS = end of study; Fg = fibrinogen; IM = intramuscular; IV = intravenous; PD = pharmacodynamic; PK = pharmacokinetic; PT = prothrombin time; RC-P = Recombinant Crisantaspase produced in *Pseudomonas fluorescens;* WBC = white blood cells.

APPENDIX 2. PART A/PART B PHARMACOKINETIC, PHARMACODYNAMIC, AND IMMUNOGENICITY SAMPLING SCHEDULE FOR IM OR IV RC-P PATIENTS

		Day	**1 (M)**	**3 (W)**	**5 (F)**	**8 (M)**	**10 (W)**	**12 (F)**	**EOS**
M/W/F	**RC-P Dosing**		**Dose 1**	**Dose 2**	**Dose 3**	**Dose 4**	**Dose 5**	**Dose 6**	-
Course 1	Cohorts	PK (SAA)	0h (predose 1); 2.5h postdose 1[a]	48h postdose 1 (predose 2)	48h postdose 2 (predose 3)	72h postdose 3 (predose 4), 2.5h postdose 4[a]	48h postdose 4 (predose 5)	48h postdose 5 (predose 6)	-
		PK (Content)[b]	0h (predose 1); 2.5h postdose 1[a]	48h postdose 1 (predose 2)	48h postdose 2 (predose 3)	72h postdose 3 (predose 4), 2.5h postdose 4[a]	48h postdose 4 (predose 5)	48h postdose 5 (predose 6)	-
		PD (Asparagine, Glutamine)	0h (predose 1); 2.5h postdose 1[a]	48h postdose 1 (predose 2)	48h postdose 2 (predose 3)	72h postdose 3 (predose 4), 2.5h postdose 4[a]	48h postdose 4 (predose 5)	48h postdose 5 (predose 6)	-
		ADA[c]	0h (predose 1)	-	-	-	-	48h postdose 5 (pre-dose 6)	-
Subsequent Courses (for both Cohorts 1 & 2)		PK (SAA)	0h (predose 1)	-	-	72h postdose 3 (predose 4)	-	48h postdose 5 (pre-dose 6)	EOS[d]
		PK (Content)[b]	0h (predose 1)	-	-	72h postdose 3 (predose 4)	-	48h postdose 5 (pre-dose 6)	EOS[d]
		PD (Asparagine, Glutamine)	0h (predose 1)	-	-	72h postdose 3 (predose 4)	-	48h postdose 5 (predose 6)	EOS[d]
		ADA[c]	0h (predose 1)	-	-	-	-	-	EOS[d]
		Day	**1 (W)**	**3 (F)**	**6 (M)**	**8 (W)**	**10 (F)**	**13 (M)**	**EOS**
W/F/M	**RC-P Dosing**		**Dose 1**	**Dose 2**	**Dose 3**	**Dose 4**	**Dose 5**	**Dose 6**	-
Course 1	Cohorts	PK (SAA)	0h (predose 1); 2.5h postdose 1[a]	48h postdose 1 (predose 2)	72h postdose 2 (predose 3)	48h postdose 3 (predose 4), 2.5h postdose 4[a]	48h postdose 4 (predose 5)	72h postdose 5 (predose 6)	-
		PK (Content)[b]	0h (predose 1); 2.5h postdose 1[a]	48h postdose 1 (predose 2)	72h postdose 2 (predose 3)	48h postdose 3 (predose 4), 2.5h postdose 4[a]	48h postdose 4 (predose 5)	72h postdose 5 (predose 6)	
		PD (Asparagine, Glutamine)	0h (predose 1); 2.5h postdose 1[a]	48h postdose 1 (predose 2)	72h postdose 2 (predose 3)	48h postdose 3 (predose 4), 2.5h postdose 4[a]	48h postdose 4 (predose 5)	72h postdose5 (predose 6)	-
		ADA[c]	0h (predose 1)	-	-	-	-	72h postdose 5 (predose 6)	-

Subsequent Courses (for both Cohorts 1 & 2		PK (SAA)	0h (predose 1)	-	-	-	48h postdose 4 (predose 5)	72h postdose 5 (predose 6)	EOS[d]
		PK (Content)[b]	0h (predose 1)	-	-	-	48h postdose 4 (predose 5)	72h postdose 5 (predose 6)	
		PD	0h (predose 1)	-	-	-	48h postdose 4 (predose 5)	72h postdose 5 (predose 6)	EOS[d]
		ADA[c]	0h (predose 1)	-	-	-	-	-	EOS[d]
		Day	**1 (F)**	**4 (M)**	**6 (W)**	**8 (F)**	**11 (M)**	**13 (W)**	**EOS**
F/M/W	**RC-P Dosing**		**Dose 1**	**Dose 2**	**Dose 3**	**Dose 4**	**Dose 5**	**Dose 6**	
Course 1	C o h o r t s	PK (SAA)	0h (predose 1); 2.5h postdose 1[a]	72h postdose 1 (predose 2)	48h postdose 2 (predose 3)	48h postdose 3 (predose 4), 2.5h postdose 4[a]	72h postdose 4 (predose 5)	48h postdose 5 (predose 6)	-
		PK (Content)[b]	0h (predose 1); 2.5h postdose 1[a]	72h postdose 1 (predose 2)	48h postdose 2 (predose 3)	48h postdose 3 (predose 4), 2.5h postdose 4[a]	72h postdose 4 (predose 5)	48h postdose 5 (predose 6)	
		PD (Asparagine, Glutamine)	0h (predose 1); 2.5h postdose 1[a]	72h postdose 1 (predose 2)	48h postdose 2 (predose 3)	48h postdose 3 (predose 4), 2.5h postdose 4[a]	72h postdose 4 (predose 5)	48h postdose 5 (predose 6)	-
		ADA[c]	0h (predose 1)	-	-	-	-	48h postdose 5 (predose 6)	-
Subsequent Courses (for both Cohorts 1 & 2		PK (SAA)	0h (predose 1)	-	-	-	72h postdose 4 (predose 5)	48h postdose 5 (predose 6)	EOS[d]
		PK (Content)[b]	0h (predose 1)	-	-	-	72h postdose 4 (predose 5)	48h postdose 5 (predose 6)	EOS[d]
		PD	0h (predose 1)	-	-	-	72h postdose 4 (predose 5)	48h postdose 5 (predose 6)	EOS[d]
		ADA[c]	0h (predose 1)	-	-	-	-	-	EOS[d]

[a] The sampling schedule for IM and IV RC-P drug administration is the same except that the 2.5 hour postdose sample is only collected for IM administration; for IV administration, an end of infusion sample is collected at approximately 2 hours post the start of infusion.

[b] PK (Content) is the same as serum asparaginase concentration.

[c] Additional samples to test for ADA may be obtained if a patient experiences an allergic reaction. If it is determined that a patient has sub-therapeutic NSAA levels (< 0.1 IU/mL), a test for ADA may be performed if there is a blood sample available. In addition, for patients who exhibit positive ADA from samples obtained prior to the end of study (30 days after a patient's final RC-P course), efforts will be made to collect follow-up ADA samples up to approximately 6 months after a patient's last dose of their last course of RC-P. For these ADA positive patients, their follow-up ADA samples will be their End of Study samples. If all required assessments are completed and there is serum remaining from any of the sample types, additional immunogenicity testing may be performed.

[d] If a patient has only one course of RC-P, EOS samples (PK, PD, and ADA) will be collected after Course 1.

Notes: All postdose samples must be collected prior to the subsequent RC-P dose. For IV administration all of the time points shown above are relative to start of infusion (ie, postdose = post start of infusion for IV).

PK/PD Time Windows are Listed Below:

Part A IM:

2.5 hours postdose: ± 15 minutes
48 hours postdose: ± 2 hours
72 hours postdose: ± 2 hours

Part B IV (administration is a 2 hour infusion):

EOI at 2 hours post start of infusion: + 15 minutes
48 hours postdose: ± 2 hours
72 hours postdose: ± 2 hours

Window for immunogenicity samples = ± 2 hours.

Abbreviations: ADA = anti-RC-P antibodies; EOS = end of study; IM = intramuscular; IV = intravenous; PD = pharmacodynamics; PK = pharmacokinetic; RC-P = Recombinant Crisantaspase produced in *Pseudomonas fluorescens*

APPENDIX 3. SUMMARY OF CHANGES

Amendment 02

Amendment 02 was initiated to allow additional higher dose subcohorts to be investigated if warranted by the data. Following is a list of the important changes in Amendment 02. Editorial changes and changes that do not impact patient care or safety are not included in this list. The following changes were also applied to the text in the synopsis.

Section Number of First Occurrence	Description of Change	Brief Rationale
Section 1.4	Allow testing of additional subcohorts at higher doses above 37.5 mg/m^2 with each additional dose level(s) not to exceed a 50% increase from the previous dose level.	The dose cap of 80 mg/m^2 was removed because the available preliminary PK modeling data has shown that higher doses than 80 mg/m^2 may be necessary to achieve the objectives of the current protocol. The current plan to not exceed a 50% increase from the previous dose level with each additional dose level and the safety monitoring outlined in the protocol are appropriate to ensure patient safety in the study.
Sections 6.7.3.2 and 6.7.5	Standardized the testing window from 3 to 7 days for all laboratory tests, including coagulation tests and laboratory tests at Screening.	To clarify the timing of the testing window for laboratory tests at study sites.

Amendment 01

Amendment 01 was initiated to allow additional dose subcohorts to be investigated if warranted by the data, and to allow Part B to be conducted in parallel with Part A. Following is a list of the important changes in Amendment 01. Editorial changes and changes that do not impact patient care or safety are not included in this list. The following changes were also applied to the text in the synopsis.

Section Number of First Occurrence	Description of Change	Brief Rationale
Section 1.4	Allow testing of additional subcohorts at higher doses above 37.5 mg/m^2 with each additional dose level(s) not to exceed a 50% increase from the previous dose	The cap of 80 mg/m^2 is based on the available preliminary PK modeling data.

Section Number of First Occurrence	Description of Change	Brief Rationale
	level and no dose level to exceed 80 mg/m^2.	
Section 3.1	Allow enrollment into Part B (IV formulation) to begin before completion of Part A (IM formulation); study center participation will be at the discretion of the Sponsor.	The IV route of administration is important, particularly in the pediatric setting, and allowing separate study centers to enroll in Part B while Part A is being completed will expedite a potential treatment option to address an unmet medical need.
Section 3.1.3.1	Based on all of the data, the SDRC may recommend that a different dose be given on Fridays than on Mondays and Wednesdays.	A new dose may need to be explored to ensure adequate dosage coverage for up to 72 hours.
Section 4	Removed the limit on the number of study centers and expand study globally.	Additional study centers outside of North America will be included in the study to increase the availability of the investigational product to patients.
Section 4.1, Inclusion Criterion #5	Specified that the undetectable SAA levels should be based on the lower limit of quantification, as defined by a certified laboratory authorized under CLIA to perform this testing.	CLIA-certified laboratories utilize different limits of quantification depending on their assay methodologies, and results to determine undetectable SAA levels may vary between laboratories.
Section 6.6	Indicated that serum asparaginase concentration is the same as PK Content for this study.	Created alignment between the SAP (which uses serum asparaginase concentration) and the label on the laboratory tubes (which uses PK Content).
Section 6.7.1	Removed time window for collection of vital signs.	The assessment of vital signs within 15 minutes of the pre-dose sample collections is not consistent with typical clinical practice, particularly in the setting of a busy pediatric hematology oncology clinic.
Section 6.7.1	Removed respiratory rate as a required assessment; respiratory rate may be collected if it is a standard of care at the study center.	The collection of respiratory rate is not a standard assessment preferred in the patient population.
Section 6.7.3.2	Updated coagulation collection language to match SOE tables.	Corrected a discrepancy in the original protocol.
Section 6.7.8	Added list of AEs that would be considered anticipated.	This list was added as a request from FDA to provide clarity for expedited safety reporting.

Section Number of First Occurrence	Description of Change	Brief Rationale
Section 8.3	Added language to the sample size calculation regarding the minimum number of patients needed for the primary and key secondary endpoints.	Additional language added for consistency with the SAP.
Section 8.4	Added the definition for the PD Analysis Set.	Added for consistency with SAP.
Appendix 1	Removed weight at the EOS visit in the Wednesday and Friday start day SOE tables.	Updated to align with the language provided in a previous Administrative Letter (and for alignment with the Monday SOE table).
Appendix 2	Created separate rows for PK (SAA) and PK (Content).	Multiple PK kits are needed at each of the specified timepoints.

Abbreviations: AE = adverse event; CLIA = Clinical Laboratory Improvement Amendments; EOS = end of study; FDA = Food and Drug Administration; IM = intramuscular; IV = intravenous; PD = pharmacodynamic; PK = pharmacokinetic; SAA = serum asparaginase activity; SAP = Statistical Analysis Plan; SDRC = Study Data Review Committee; SOE = schedule of events.

APPENDIX 4. SIGNATURES OF AGREEMENT, PROTOCOL AMENDMENT 02

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

Study Number: JZP458-201

Final Date Protocol: 03 September 2020

This clinical study protocol was subjected to critical review and has been approved by Jazz Pharmaceuticals.

Signed: {Please see appended electronic signature page} Date:_____
[redacted] MD
Executive Medical Director
Hematology/Oncology Therapeutic Area
Medical Monitor
Jazz Pharmaceuticals

Signed: {Please see appended electronic signature page} Date:_____
[redacted]
Director, Clinical Science
Clinical Development, Hematology/Oncology Therapeutic Area
Medical Monitor
Jazz Pharmaceuticals

Signed: {Please see appended electronic signature page} Date:_____
[redacted] PhD
Director, Clinical Pharmacology
Jazz Pharmaceuticals

Signed: {Please see appended electronic signature page} Date:_____
[redacted]
Director, Regulatory Strategy
Regulatory Affairs
Jazz Pharmaceuticals

Signed: {Please see appended electronic signature page} Date:_____
[redacted] PhD
Senior Manager, Biostatistics
Jazz Pharmaceuticals