Official Title: A Phase 2 Clinical Study of SHP674 in Patients with Newly Diagnosed, Untreated Acute Lymphoblastic Leukemia

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STATISTICAL ANALYSIS PLAN

SHP674-201

A PHASE 2 CLINICAL STUDY OF SHP674 IN PATIENTS WITH NEWLY DIAGNOSED, UNTREATED ACUTE LYMPHOBLASTIC LEUKEMIA

AUTHOR: [redacted]

VERSION NUMBER AND DATE: V2.0, 02APR2021

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan V2.0 (Dated 02APR2021) for Protocol SHP674-201.

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Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

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MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
1.0	27AUG2018	[redacted]	Not Applicable – First Version
2.0	02APR2021	[redacted]	- Changed the definition of the baseline - Added summary related to COVID-19 - Added Section 15.1. CONCOMITANT MEDICATIONS FOR ALLERGY PREVENTION OF SHP674 - Added Section 23. REFERENCES - Added APPENDIX 3. FIRST ANALYSIS DATA CUT-OFF PLAN

TABLE OF CONTENTS

1. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of efficacy, safety, pharmacokinetic (PK) and immunogenicity data for Protocol SHP674-201. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed.
This statistical analysis plan (SAP) is based on protocol version 1.5, dated 22Jan2021.

2. STUDY OBJECTIVES

Refer to Section 4.1.1 and 4.1.2 for definition of "Part 1" and "Part 2".

2.1. PRIMARY OBJECTIVE

2.1.1. PART 1

To assess the tolerability and safety of a single dose of SHP674 in subjects with newly diagnosed, untreated acute lymphoblastic leukemia (ALL) in the tolerability assessment period.

2.1.2. PART 2

To assess the percentage of subjects with newly diagnosed, untreated ALL who have a plasma asparaginase activity of >=0.1 IU/mL 14 days (336 hours) after the first dose of SHP674.

2.2. SECONDARY OBJECTIVES

2.2.1. PART 1

- To assess the percentage of subjects with newly diagnosed, untreated ALL who have a plasma asparaginase activity of >=0.1 IU/mL 14 days (336 hours) after the first dose of SHP674.
- To assess the safety of SHP674.
- To assess the PK of SHP674.
- To assess the immunogenicity of SHP674.
- To assess the survival rate at 1 year after the start of study treatment.
- To assess the event-free survival rate at 1 year after the start of study treatment.

2.2.2. PART 2

- To assess the safety of SHP674.
- To assess the PK of SHP674.
- To assess the immunogenicity of SHP674.
- To assess the survival rate at 1 year after the start of study treatment.
- To assess the event-free survival rate at 1 year after the start of study treatment.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

3. ENDPOINTS

3.1. PRIMARY ENDPOINTS

3.1.1. PART 1

Incidence and nature of treatment-emergent adverse events (TEAEs) and SHP674-related TEAEs that occur or worsen during the tolerability assessment period.

3.1.2. PART 2

Achievement of a plasma asparaginase activity of >=0.1 IU/mL 14 days (336 hours) after the first dose of SHP674.

3.2. RATIONALE FOR THE PRIMARY ENDPOINT

3.2.1. PART 1

The current dose of SHP674 has been confirmed in multiple clinical studies overseas. Based on the characteristics of the drug (i.e., large protein), ethnic factors (genetic polymorphisms etc.) are not expected to affect the dose of the drug in the Japanese patients. Part 1 of the study is intended to confirm the tolerability of the established dose in the Japanese population. TEAEs and SHP674-related TEAEs have been selected as the primary endpoint to assess the tolerability and safety of SHP674 in Japanese patients.

3.2.2. PART 2

Plasma or serum asparaginase activity is an effective surrogate endpoint for clinical efficacy, and a plasma or serum asparaginase activity of >=0.1 IU/mL is the threshold for securing sustained asparagine depletion. In the foreign clinical studies, achievement of a plasma asparaginase activity of >=0.1 IU/mL after the administration of SHP674 was used as an endpoint. The dosing interval of SHP674 stated in the package insert in Europe is 14 days. Thus, the percentage of subjects who have a plasma asparaginase activity of >=0.1 IU/mL 14 days after the administration of SHP674 has been selected as the primary endpoint of the present study to demonstrate the efficacy of SHP674 similar to that shown in the foreign studies.

3.3. SECONDARY ENDPOINTS

3.3.1. PART 1

- Safety
    - Incidence and nature of TEAEs and drug-related TEAEs
    - Laboratory values
    - Vital signs
- PK
    - PK parameters
- Immunogenicity

- anti-SHP674 antibody (ADA) and anti-polyethylene glycol (PEG) antibody

- Efficacy
  - Achievement of a plasma asparaginase activity of >=0.1 IU/mL 14 days (336 hours) after the first dose of SHP674.
  - Survival rate at 1 year after the start of study treatment
  - Event-free survival rate at 1 year after the start of study treatment

3.3.2. PART 2

- Safety
  - Incidence and nature of TEAEs and drug-related TEAEs
  - Laboratory values
  - Vital signs
- PK
  - PK parameters
- Immunogenicity
  - ADA and anti-PEG antibody
- Efficacy
  - Plasma asparaginase activity
  - Survival rate at 1 year after the start of study treatment
  - Event-free survival rate at 1 year after the start of study treatment

[redacted]

[redacted]

[redacted]

[redacted] [redacted]

[redacted]

4. STUDY DESIGN

4.1. GENERAL DESCRIPTION

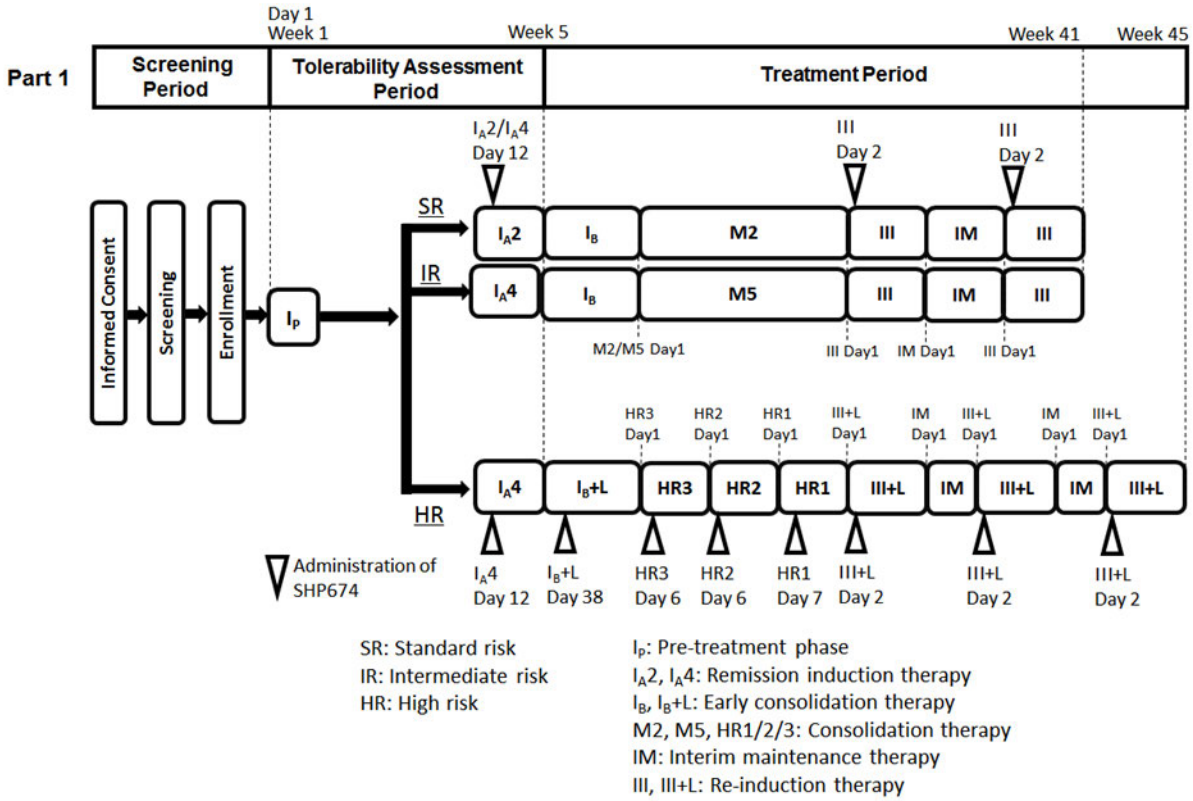
This is a multicenter, non-randomized, open-label, Phase 2 clinical study of SHP674 in Japanese subjects with newly diagnosed, untreated ALL. The study consists of Part 1 and Part 2.
In this study, the date of starting prednisolone administration in the pre-treatment phase (I_P) is defined as Day 1. Days of each treatment phase or block are defined in the protocol. The week when the pre-treatment phase is started is defined as Week 1. The week preceding the start week of the pre-treatment phase is defined as Week 0. The week that is Y weeks after the start of the pre-treatment period will be regarded as Week Y. As a general rule, subjects will be hospitalized during remission induction therapy (I_A2/I_A4).

4.1.1. PART 1

Part 1 is comprised of a screening period and a subsequent tolerability assessment period (from the pre-treatment phase through remission induction therapy [Day 1 to Day 37]; for at least 25 days after the first dose of SHP674) and a treatment period (from early consolidation therapy to the end-of-study assessment). Subjects categorized as standard risk (SR) or intermediate risk (IR) will receive a total of 3 doses of SHP674 and those categorized as high risk (HR) will receive a total of 8 doses of SHP674 during the tolerability assessment period and the treatment period (the details of risk classification SR, IR and HR are described in Section 3.1.3 of the protocol). The outline of the study design in Part 1 is shown in the Figure 1. The tolerability assessment period consists of a pre-treatment phase (I_P) and remission induction therapy (I_A2/I_A4) according to the regimen used in Study ALL-B12. The treatment period consists of early consolidation therapy (I_B/I_B+L), consolidation therapy (M2/M5/HR3, HR2, HR1), re-induction therapy (III/III+L), and interim maintenance therapy (IM), which are also based on the regimen used in Study ALL-B12. Subjects who complete the tolerability assessment period will move to the treatment period and continue to receive SHP674. The outline of each treatment phase is shown in Figure 3.
Subjects will undergo screening after giving informed consent, and eligible subjects will be enrolled within 21 days after giving informed consent and within 14 days after screening. Subjects will start treatment within 7 days after enrollment. Only subjects who are able to give assent or informed consent will be enrolled in Part 1.
Part 1 will enroll 3 to 6 subjects who give informed assent or written informed consent to assess tolerability. The

tolerability assessment will be based on the number of subjects who experience intolerable toxicity during the tolerability assessment period (the details of the assessment method are described in Section 7.5.4 of the protocol). Safety data of Part 1 will be reviewed by an internal safety committee (composed of the sponsor and study investigators) that will determine if the dose investigated in Part 1 was well tolerated and Part 2 can be initiated with this dose.

Figure 1: Outline of Study Design in Part 1



4.1.2. PART 2

Part 2 is comprised of a screening period and a subsequent treatment period (from the pre-treatment phase to the end-of-study assessment). Subjects categorized as SR or IR will receive 3 doses of SHP674 and those categorized as HR will receive 8 doses of SHP674 during the treatment period. The outline of the study design in Part 2 is shown in the Figure 2. The treatment period consists of a pre-treatment phase (I_P), remission induction therapy (I_A2/I_A4), early consolidation therapy (I_B/I_B+L), consolidation therapy (M2/M5/HR3, HR2, HR1), re-induction therapy (III/III+L), and interim maintenance therapy (IM) according to the regimen used in Study ALL-B12. The outline of each treatment phase is shown in Figure 3.

Subjects will undergo screening after giving informed consent, and eligible subjects will be enrolled within 21 days after giving informed consent and within 14 days after screening. Subjects will start treatment within 7 days after enrollment.

Part 2 will target to enroll 22 subjects to evaluate the efficacy, safety, and PK of SHP674 at the dose shown to be tolerated in Part 1.

Figure 2: Outline of Study Design in Part 2

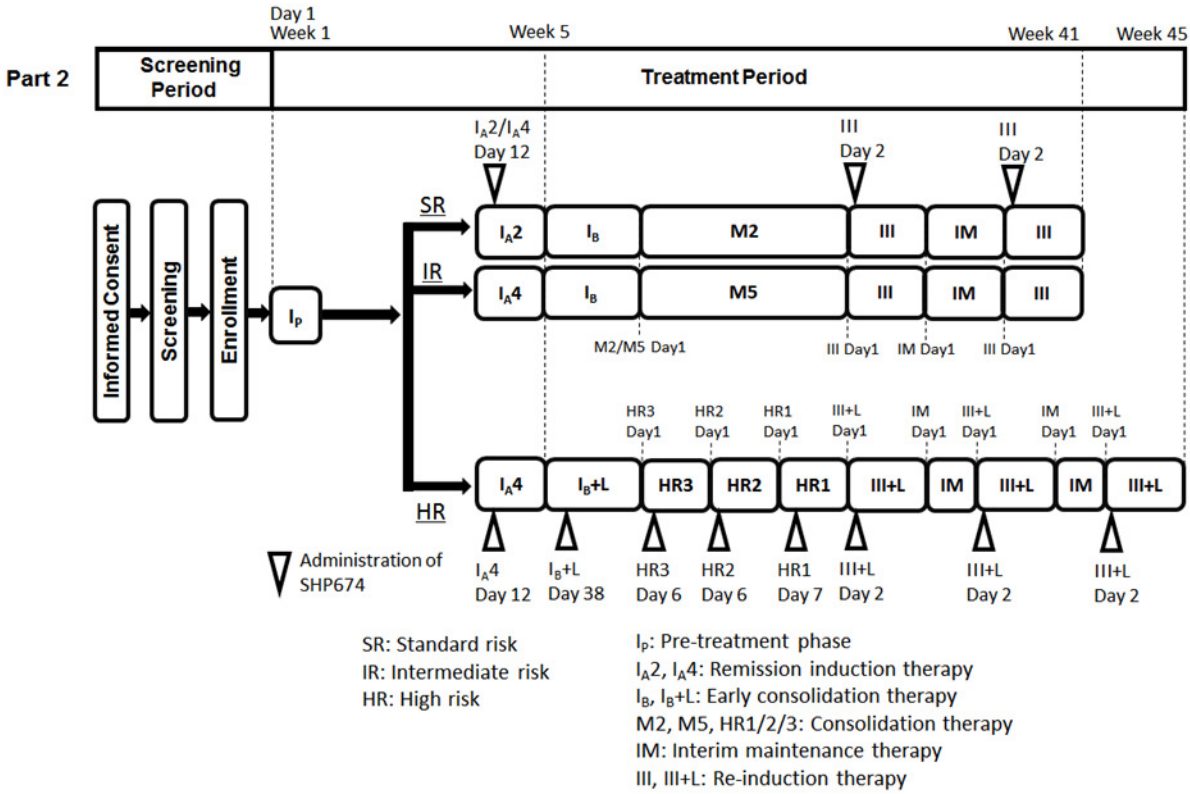
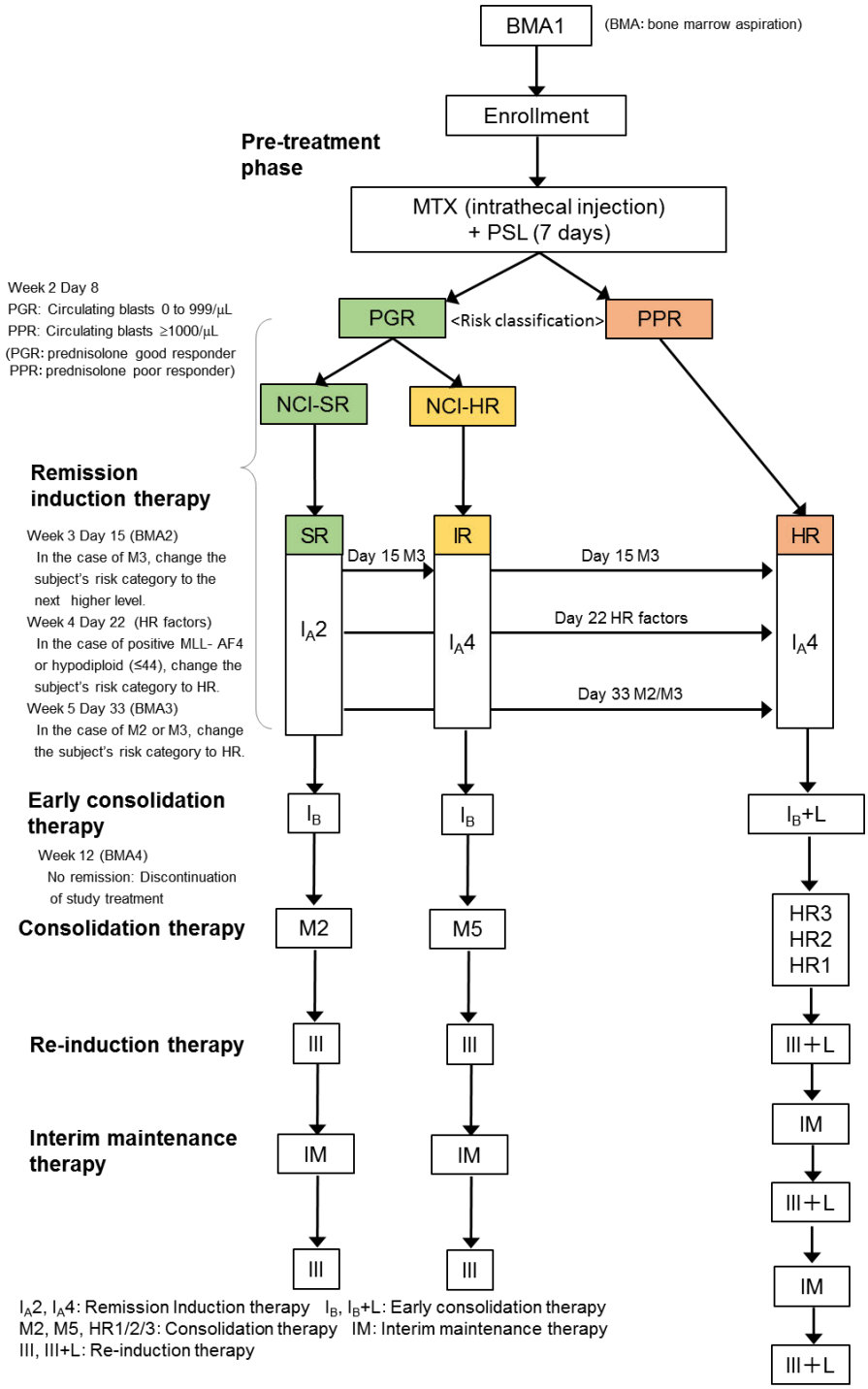


Figure 3: Outline of Each Treatment Phase



4.1.3. TARGET SAMPLE SIZE

Part 1: 3 to 6 evaluable subjects
Part 2: 22 subjects

4.1.3.1. Rationale for Target Sample Size

Leukemia is the most common pediatric malignancy. ALL is the most common type (46.6%) of acute leukemia in childhood, and 500 children are newly diagnosed with ALL each year in Japan.
Precursor B-cell ALL, which is the target disease of this study, accounts for 85.6% of all pediatric ALL. Therefore, the number of patients in the target population of this study is estimated to be approximately 428 per year. The target sample size for Part 2 of the study has been set at 22, based on the estimated number of subjects who meet the eligibility criteria in the protocol, study feasibility, information on subject accrual provided by the Japanese Pediatric Leukemia/Lymphoma Study Group (JPLSG), limited number of investigative sites, and the rate of informed consent.
The appropriateness of setting the target sample size at 22 was determined based on the percentage of subjects who achieve a plasma asparaginase activity of >=0.1 IU/mL 14 days (336 hours) after the first dose of SHP674, which is the expected level in this study, and the corresponding 95% confidence interval. The percentages of subjects with a plasma asparaginase activity of 0.1 IU/mL and the corresponding exact 95% confidence intervals in clinical studies of SHP674 conducted outside Japan (Studies AALL07P4, DFCI 11-011, and CCG-1962, the details of these studies are described in Section 1.5.1 of the protocol) were 100.0% (50/50 subjects) (95% CI: 92.9%, 100.0%) in Study AALL07P4, 93.8% (45/48 subjects) (95% CI: 82.8%, 98.7%) in Study CCG-1962, and 98.2% (111/113 subjects) (95% CI: 92.9%, 100.0%) in Study DFCI 11-001. On the basis of these results, the percentage of subjects achieving a plasma asparaginase activity of >=0.1 IU/mL 14 days (336 hours) after the first dose of SHP674, the expected level in this study, was estimated to be around 90%. If the expected percentage is 90.9% (20/22 subjects) in this study, a target sample size of 22 would provide an exact 95% confidence interval of 70.8% to 98.9%.
Since this is the first study of SHP674 in Japanese patients, 3 to 6 subjects will be enrolled in Part 1 of the study for tolerability assessment, separately from the above 22 subjects.

4.2. SCHEDULE OF EVENTS

Treatment schedules can be found in Table 7-1 to Table 7-3 in Section 7 of the protocol.
Other study procedures can be found in Table 8-1 to Table 8-3 in Section 8 of the protocol.

4.3. CHANGES TO ANALYSIS FROM PROTOCOL

There are no changes to analysis from protocol.

5. PLANNED ANALYSES

The following analyses will be performed for this study:

- Evaluation of tolerability by the internal safety committee
- First analysis after all subjects complete remission induction therapy (for Clinical study report (CSR))
- Final analysis at the end of this study (for CSR addendum)

This document does not describe evaluation of tolerability by the internal safety committee to determine whether the dose investigated in Part 1 was well tolerated and Part 2 can be initiated with the dose.

First and final analyses identified in this SAP will be performed by IQVIA Biostatistics following Sponsor Authorization of this Statistical Analysis Plan, Database Lock, and Sponsor Authorization of Analysis Sets.

5.1. INTERIM ANALYSIS

No interim analysis is planned for this study.

5.2. FIRST ANALYSIS AND FINAL ANALYSIS

First analysis: This analysis will be performed after all patients complete remission induction therapy. CSR will be based on the data from the period of remission induction phase (the details of data cut off are described in Section 12.7 of the protocol). The first analysis will not include [redacted] long term survival analysis such as Overall Survival (OS) and Event-free Survival (EFS).
See Appendix 3 for first analysis data cut-off plan.

Final analysis: This analysis will be performed at the end of study. Analysis results will be included in the CSR addendum. Data from subsequent treatment periods in the study will be part of the final analysis that will be performed at the time of completion of study, which will occur 365 (±7) days after the first dose of SHP674 in the last subject or at the time when all subjects complete the study. The final analysis will include [redacted] long term survival analysis such as OS and EFS.

Unless otherwise specified, all statistical analyses planned in this document will be performed at "First analysis".

6. ANALYSIS SETS

Agreement and authorization of subjects included/ excluded from each analysis set will be conducted prior to the database lock at the first analysis of the study.
The number and percentage of subjects in analysis set, exclusions will be summarized by all subjects.

6.1. ALL ENROLLED SET [ENR]

The all enrolled set (ENR) will consist of all patients who have provided informed consent in the study.

6.2. SAFETY ANALYSIS SET [SAF]

The safety analysis set (SAF) is defined as the set of all subjects who have received at least one dose of SHP674 in Part 1 or Part 2 of study. The safety endpoints will be analyzed in the safety analysis set.
All safety analyses will be performed separately for Part 1 and Part 2 of study as well as for the combination of Parts 1 and 2 resulting in all patients dosed in the study.
Descriptive analyses on efficacy endpoints in Part 1 will be based on the safety analysis set.

6.3. FULL ANALYSIS SET [FAS]

The full analysis set (FAS) is defined as a set of all subjects who are enrolled and receive SHP674 in Part 2 of the study. All efficacy analyses (including primary analysis) in Part 2 will be based on the full analysis set.

6.4. IMMUNOGENICITY ANALYSIS SET [IMAS]

The immunogenicity analysis set (IMAS) is defined as the set of all subjects who have received at least one dose of SHP674 in Part 1 or Part 2 of the study and have at least one evaluable post-dose sample. In the case of immunogenicity if the pre-dose sample is missing it will be considered negative.
All immunogenicity analyses will be performed separately for Part 1 and Part 2 of the study as well as for the combination of Parts 1 and 2 resulting in all patients dosed in the study.

6.5. PK ANALYSIS SET [PKAS]

The PK analysis set (PKAS) is defined as all subjects enrolled in Part 1 or Part 2 who have received first dose of SHP674 at remission induction therapy and who are evaluable for non-compartmental analysis. The PK dataset will include only the subjects who had sufficient samples collected to provide interpretable PK results with no deviations that might have affected the PK interpretation.

7. GENERAL CONSIDERATIONS

7.1. REFERENCE START DATE AND STUDY DAY

Study Day will be calculated from the reference start date, and will be used to show start/ stop day of assessments and events.
Reference start date is defined as the start date of pre-treatment phase (I_P), (Day 1 is the first day of pre-treatment phase), and will appear in every listing where an assessment date or event date appears.

- If the date of the event is on or after the reference start date then:

  Study Day = (date of event - reference start date) + 1.

- If the date of the event is prior to the reference start date then:

  Study Day = (date of event - reference start date).

In the situation where the event date is partial or missing, Study Day, and any corresponding durations will appear missing in the listings.

7.2. BASELINE

Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to the date of starting prednisolone administration in the pre-treatment phase (including unscheduled assessments).

7.3. DERIVED TIMEPOINTS

No derived time points will be utilized for this study.

7.4. UNSCHEDULED VISITS AND EARLY TERMINATION DATA

In general, for by-visit summaries, data recorded at the nominal visit will be presented. Unscheduled measurements will not be included in by-visit summaries.
Listings will include scheduled, unscheduled, and early discontinuation data.

7.5. WINDOWING CONVENTIONS

Analysis for Non-PK data:
There is no visit windowing for this study. Instead, all analyses will use all scheduled visits recorded on the electronic case report form (eCRF).

Analysis for PK data:
The time windows provided in Table 8.22.1-1 of the protocol will be used for the purpose of summarizing concentrations. If samples are taken outside of the window, the concentration will be excluded from summaries but will be included in the PK parameter calculations since they are based on actual elapsed sampling time.

7.6. STATISTICAL TESTS

Hypothesis testing will not be performed. Confidence intervals (CIs) for estimations will be 95%. The default significant level will be 5%; CIs will be 95% and all tests will be two-sided, unless otherwise specified in the description of the analyses.

7.7. DESCRIPTIVE STATISTICS

Qualitative measurements will be summarized with number of subjects and percentage.
Quantitative measurements will be summarized with the following descriptive statistics: number of observations (n), mean, standard deviation (SD), median, minimum, and maximum.
Descriptive statistics of PK concentrations will be n, mean, SD, median, minimum, maximum, and coefficient of variation (CV%). Descriptive statistics of PK parameters will also include geometric mean and geometric CV%.
An n >= 2 will be required for calculations of descriptive statistics. If n = 1, only n and mean will be presented. If n = 0, only n will be presented, and descriptive statistics will be set to missing.

7.8. PRECISION

All PK concentrations will be reported and analyzed with the same precision as the source data provided by the bioanalytical laboratory regardless of how many significant figures or decimals the data carry.
Derived PK parameters will be rounded to three significant digits for listings, except t_{max} which will be rounded to 2 decimal places. The unrounded derived PK parameters will be used for the calculation of descriptive statistics and the statistical analysis.
For the reporting of descriptive statistics, means and median will be presented to 1 significant digit or decimal more precision than the source data. Standard deviation will be presented to 2 more digits or decimal places than the source data. Minimum and maximum will be presented to the same precision as the source data. Coefficient of variation will be presented to 1 decimal place. Percentages will be reported to 1 decimal place. Confidence intervals, estimates, and coefficient of determination will be presented to 2 decimal places.

7.9. SOFTWARE VERSION

All tables, listings and figures will be conducted using SAS® Version 9.4 or higher (SAS Institute Inc., Cary, North Carolina).
Pharmacokinetic parameter computations will be performed using Phoenix® WinNonlin® 8.0 or higher (Certara L.P., Princeton, New Jersey). Figures will be prepared using the same versions of SAS. The software version used for analysis will be documented in the CSR.

8. STATISTICAL CONSIDERATIONS

8.1. MULTICENTER STUDIES

This study will be conducted by multiple investigators at multiple centers within Japan.

8.2. MISSING DATA

For handling of missing immunogenicity data, see Section 20.1. For handling of missing data for calculation of the PK parameters, see Section 21.2.
Other missing data will not be imputed by a specific statistical method. Patients without evaluable Day 14 plasma asparaginase activity data will be excluded from the primary efficacy analysis.

8.3. MULTIPLE COMPARISONS/ MULTIPLICITY

Not applicable

8.4. EXAMINATION OF SUBGROUPS

Subgroup analyses will be conducted as stated in the [redacted] adverse events analysis sections (See Section 19.1.10).
The following subgroups will be assessed and described within the each analysis sections:

- Age (years) at informed consent:
  - < 10
  - >= 10
- WBC count (x10^9/L) at baseline visit:
  - < 50
  - >= 50

9. OUTPUT PRESENTATIONS

Shell provided with this SAP describe the presentations for this study and therefore the format and content of the summary tables, figures, and listings to be provided by IQVIA Biostatistics.

10. DISPOSITION AND WITHDRAWALS

Subject disposition, withdrawals and the primary reasons will be summarized by treatment phase withdrawn, part of study (Part 1, Part 2) and overall for the ENR set.
The following summaries will be provided for all subjects when applicable:

- Subjects Enrolled (who provide informed consent)
- Screening Failure, and the reason (deviated Inclusion/Exclusion criteria)
- Eligible subjects
- Eligible subjects but were not treated with SHP674
- Subject treated with SHP674

- Subjects who completed the remission induction therapy
- Subject who completed the study
- Withdrawal from the study
- Primary Reason for Withdrawal from the study
- Treatment discontinuation
- Primary Reason for Treatment discontinuation

A summary of the reasons for discontinuation associated with COVID-19 is also provided.

11. PROTOCOL DEVIATION

11.1. DEVIATION FROM PROTOCOL

All protocol deviations are recorded in the Protocol Deviation list provided by IQVIA Clinical Operations. Critical and major protocol deviations will be summarized by part of study and overall, using the number and percentage of subjects who had each type of deviation for the SAF.
COVID-19 related protocol deviation will be also summarized.
In addition, all protocol deviations (Critical, Major and Minor) will be listed.

11.2. SIGNIFICANT PROTOCOL DEVIATIONS /EVENTS RELATED TO THE PK ANALYSIS

Changes to the procedures or events, which may impact the quality of the PK data, will be considered significant protocol deviations/events related to the PK analysis and will be described within the CSR body text. These changes or events will include any circumstances that will alter the evaluation of the PK. Example of significant protocol deviations /events related to the PK analysis include, but may not be limited to:

- Deviation from inclusion and/or exclusion criteria with potential to affect PK
- Deviation from study restrictions with potential to affect PK
- Concomitant medications that can affect PK
- Missed, incomplete, or incorrect dosing that can affect PK
- Sample handling and/or bioanalytical issues affecting PK
- Missing concentration(s) or sample(s) not collected at key times in PK profile
- Significant time deviation(s) at times in PK profile

- Anomalous pre-dose concentrations >5% of C_{max} following a remission dose administration

In the case of a significant protocol deviation/event, PK data collected during the affected treatment period will be excluded from the study results. Other changes to the procedures or events which do not impact the quality of the PK data will not be excluded from the PK analysis. A common example of a non-significant protocol deviation/event is a missed blood sample or deviations from blood collection times (that are not key times in PK profiles).
The exclusions from analysis populations resulting from deviations/events affecting PK will be specified in the evaluation of PK profiles and will be described in the CSR.

12. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics will be summarized by part of study and overall for the SAF, IMAS and PKAS. Same summarization will be done for the FAS (Part 2 only).
The following demographic and other baseline characteristics will be reported for this study:

- Age (years) at informed consent
- Category of age (years): "< 10", ">= 10"
- Sex: "Female", "Male"
- Race: "Asian"
- Weight (kg) at baseline visit
- Height (cm) at baseline visit
- Body surface area (BSA) (m^2) at baseline visit
- Category of BSA (m^2) at baseline visit: ">= 0.60 m^2", "< 0.60 m^2"
- WBC count (x10^9/L) at baseline visit
- Category of WBC count (x10^9/L) at baseline visit: "< 50", ">= 50"
- Nudix Hydrolase 15 (NUDT15) polymorphism at screening visit: "Arg/Arg", "Cys/Cys", "Homozygous genotype other than Arg/Arg and Cys/Cys or heterozygous genotype"

12.1. DERIVATIONS

- BSA (m^2) = (height (cm) /weight (kg) / 3600) $^{1/2}$
- When fitted to the above formula, height and weight will be rounded according to the following rules. If the measuring instrument of weight displays values up to one decimal place, the displayed value will be used for the calculation.

- - Height: Rounded to the nearest integer (for example, 123.1 cm => 123 cm)
- - Weight: Rounded to one decimal place (for example, 30.15 kg => 30.2 kg)
- The resulting value will be rounded to two decimal places to obtain the BSA (example 1: 1.234 m^2 => 1.23 m^2, example 2: 0.968 m^2 => 0.97 m^2).

13. PRIMARY DISEASE

Primary disease information will be summarized by part of study and overall for the SAF.
Primary disease will be included on the Primary Disease eCRF page and includes information for risk classification:

- NCI classification
    - NCI-SR
    - NCI-HR

Primary disease will be included on the Response to PSL (Prednisolone) eCRF page and includes information for steroid response at Week 2 Day 8:

- Response to PSL
    - PGR (prednisone good response)
    - PPR (prednisone poor response)
    - Primary disease summary should also include the following information:

- Genetic analysis results related to the primary disease (*KMT2A-AFF1* [*MLL-AF4*]): “Positive”, “Negative”
- Chromosome analysis results related to the primary disease (hypodiploid): “> 44”, “<= 44”

13.1. RISK CLASSIFICATION AT THE END OF REMISSION INDUCTION THERAPY

Risk classification at the end of remission induction therapy will be presented by part of study and overall for the SAF.

14. CONCURRENT DISEASES AND MEDICAL HISTORY

Concurrent diseases and medical history will be presented by part of study and overall for the SAF.

Concurrent diseases are included on the Medical History eCRF page and will be separated from medical history for summary.
Medical history of subjects will be coded by System Organ Class (SOC) and Preferred Term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) version 23.1.
Incidence and number of medical history will be presented by SOC and PT.

15. CONCOMITANT MEDICATIONS AND THERAPIES

The drug or therapy other than SHP674 or the backbone therapy drugs specified in Section 7.2.1 of the protocol will be presented for the SAF and coded using the WHO Drug Dictionary (WHO-DD), Version 01Sep2019.
Concomitant medications and therapies are defined as those received between the day of informed consent and the end of the study (or early termination).
Incidence and number of concomitant medications will be presented by primary ATC level.
Concomitant medications will be listed for SAF. The list of concomitant medications and therapies will be prepared.

15.1. CONCOMITANT MEDICATIONS FOR ALLERGY PREVENTION OF SHP674

The analyses described in Section 15 will be presented for concomitant medications for allergy prevention of SHP674.
Concomitant medications for allergy prevention of SHP674 will be identified using the words “ALLERGY TO SHP674” in the “Indication: Prevention - Specify” from the Concomitant Medications (other than study treatment) page of the eCRF.

16. TEST DRUG (SHP674) EXPOSURE

Exposure to test drug will be summarized for SAF.
The following will be summarized using descriptive statistics by part of study and overall, and risk group at the end of remission induction therapy ("SR&IR", "HR"):

- Duration of exposure, calculated as (date of last dose - date of first dose + 1)
- Cumulative exposure (IU), calculated as (sum of the doses)
- Number of doses, calculated as (total number of doses)

Exposure to test drug will be listed for SAF.

The date and time of test drug administration will be taken from the eCRF Exposure (SHP674) form.

17. BACKBONE THERAPY DRUGS EXPOSURE

The backbone therapy drugs specified in Section 7.2.1 of the protocol will be listed for ENR.
The date and time of backbone therapy drugs administration will be taken from the each eCRF Exposure form.

18. EFFICACY ANALYSIS

All outputs for efficacy analysis will be based on the FAS as primary and secondary endpoint in Part 2. In addition, the same analysis using all SAF patients who received the Part 2 dose will be performed separately as supportive analysis.

18.1. PRIMARY EFFICACY

The number and percentage of subjects with a plasma asparaginase activity of >=0.1 IU/mL at 14 days (336 hours) after the first dose of SHP674 will be calculated in Part 2.
The corresponding 95% CIs will be calculated based on clopper pearson method.

18.2. SECONDARY EFFICACY

18.2.1. PLASMA ASPARAGINASE ACTIVITY

The number and percentage of subjects with a plasma asparaginase activity of >=0.1 IU/mL or <0.1 IU/mL at each time point will be calculated.
The corresponding 95% CIs will be calculated.

18.2.2. OVERALL SURVIVAL (OS)

18.2.2.1. Variables & Derivation

Time from the day of the first dose of SHP674 until death from any cause will be defined as OS time.

OS time (days) = (date of death/censoring - date of first dose of SHP674) + 1.

The date of death from any cause will be identified by using “Date of Death” from the Survival Follow-up page of

the eCRF.

In the absence of confirmation of death, survival time will be censored at the last date of follow-up when the subject was known to be alive. The censoring date will be identified by using "Date of Last Survival Confirmed" or "Date of Confirmed" from the Survival Follow-up page of the eCRF.

18.2.2.2. Analysis

The overall survival rate at 1 year (1 year is defined as 365 days) after the first dose of SHP674 will be calculated as Kaplan-Meier estimate and 95% CI for survival function.

A summary and a plot of the Kaplan-Meier estimates of the survival function will be provided along with the number at risk. The quartiles and median of the survival times will also be estimated. The 95% CIs for the survival function and the 95% CIs for the quartiles and median of the survival times will be calculated using the log-log transformation method.

A listing of the survival times by subject will be created.

18.2.3. EVENT-FREE SURVIVAL (EFS)

18.2.3.1. Variables & Derivation

Time from the day of the first dose of SHP674 until any one of the following events, whichever occurs first, will be defined as EFS time:

EFS time (days) = (date of event/censoring - date of first dose of SHP674) + 1.

- Induction failure [redacted].
- Documented relapse [redacted]
- Diagnosis of a second malignant neoplasm (including myelodysplastic syndrome)
- Death from any cause

Induction failure will be specified as check for "5) The subject has no remission at bone marrow examination during early consolidation therapy (BMA4)" in "Primary Reason for Treatment discontinuation" from End of Study page of the eCRF.

Other events will be collected in "Relapse?", "Secondary Malignancy?" and "Die?" from Survival Follow-up page of eCRF.

In the absence of a documented EFS event as defined above, EFS is to be censored on the date of last evaluation.

18.2.3.2. Analysis

The event-free survival rate at 1 year (1 year is defined as 365 days) after the first dose of SHP674 will be calculated as Kaplan-Meier estimate and 95% CI for survival function.

A summary and a plot of the Kaplan-Meier estimates of the survival function will be provided along with the number at risk. The quartiles and median of the survival times will also be estimated. The 95% CIs for the survival function and the 95% CIs for the quartiles and median of the survival times will be calculated using the log-log transformation method.

A listing of the survival times by subject will be created.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

19. SAFETY ANALYSIS

All outputs for safety analysis will be based on the SAF.

All safety analyses will be performed separately for Part 1 and Part 2 of study as well as for the combination of Parts 1 and 2 resulting in all patients dosed in the study.

19.1. ADVERSE EVENTS

Adverse Events (AEs) will be coded using Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary, Version 23.1.

Any partial dates for AEs will not be imputed as described in Section 8.2.

AEs are classified according to the timing of onset date as follows:

Definition	Period	Period Start	Period End	AE Type
AE	Pre-treatment period	Screening	Day 1	Pre-treatment AEs

TEAE	Pre SHP674 treatment period	Day 1	Day 12 (prior to first dose of SHP674)	Pre SHP674 TEAEs
	SHP674 treatment period	Day 12 (first dose of SHP674)	+30 days post last SHP674 dose*	SHP674 TEAEs
	Post SHP674 treatment period**	+30 days post last SHP674 dose	+30 (+7) days post last dose of concomitant investigational product*	Post SHP674 TEAEs
AE	Post treatment period	Start day of next therapy	+30 days post last dose of SHP674/concomitant investigational product	Post treatment AEs

* Or until switch to next therapy.

** Applicable if concomitant investigational products are administered after completion of SHP674 treatment or any SAE related to SHP674 or study procedure that occurs outside of defined period end for SHP674 Treatment period

See Appendix 1 for another asparaginase.

In handling the data, Pretreatment period is treated as the period from the “Informed consent” to “Day -1”, Pre SHP674 treatment period is treated as the period from “Day 1” to “Day 11”, and Post SHP674 treatment period is treated as the period starting from "+31 days post last SHP674 dose".

TEAEs (combined Pre/Post SHP674 TEAEs and SHP674 TEAEs) will be summarized.

An overall summary of number of subjects within each of the categories described in the sub-section below, will be provided.

Listings will include Any AE.

19.1.1. ALL TEAEs

Incidence and number of TEAEs will be presented by System Organ Class (SOC) and Preferred Term (PT) and also broken down further by maximum severity and relationship to test drug (SHP674).

19.1.1.1. Severity (CTCAE Grade)

Severity is classed using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

If a subject reports a TEAEs more than once within that PT, the AE with the worst-case severity will be used in the corresponding severity summaries.

19.1.1.2. Relationship to Test Drug (SHP674)

Relationship, as indicated by the Investigator, is classed as “not related” or “related”. A “related” TEAE is defined as a TEAE with a relationship to test drug as “related”. TEAEs with a missing relationship to test drug will be

regarded as "related" to test drug. If a subject reports the same AE more than once within that SOC/ PT, the AE with the most related one will be used in the corresponding relationship summaries.

19.1.2. MOST FREQUENT TEAES

TEAEs with greater than or equal to 10% incidence in all subjects will be defined as common TEAEs.
Common TEAEs will be presented by SOC and PT.

19.1.3. TEAES LEADING TO DISCONTINUATION OF TEST DRUG (SHP674)

TEAEs leading to permanent discontinuation of test drug will be identified by using "Action Taken with SHP674" of "Drug Withdrawn" from the Adverse Event page of the eCRF.
For TEAEs leading to discontinuation of test drug, summaries of incidence rates (frequencies and percentages) by SOC and PT will be prepared.

19.1.3.1. Serious/Non-Serious TEAEs Leading to Discontinuation of Test Drug (SHP674)

A summary of serious/non-serious TEAEs leading to discontinuation of test drug by SOC and PT will be prepared.

19.1.4. TEAES LEADING TO DISCONTINUATION OF BACKBONE THERAPY DRUGS (OTHER THAN SHP674)

TEAEs leading to permanent discontinuation of backbone therapy drugs will be identified by using "Action Taken with PSL (PO)", "Action Taken with PSL (IV)", "Action Taken with PSL (IT)", "Action Taken with HD-MTX", "Action Taken with MTX (PO)", "Action Taken with CPA", "Action Taken with 6-MP", "Action Taken with DEX (PO)", "Action Taken with DEX (IV)", "Action Taken with VP-16",and "Action Taken with IFO" of "Drug Withdrawn" from the Adverse Event page of the eCRF.
For TEAEs leading to discontinuation of backbone therapy drugs, summaries of incidence rates (frequencies and percentages) by SOC and PT will be prepared.

19.1.4.1. Serious/Non-Serious TEAEs Leading to Discontinuation of Backbone Therapy Drugs (other than SHP674)

A summary of serious/non-serious TEAEs leading to discontinuation of backbone therapy drugs by SOC and PT will be prepared.

19.1.5. SERIOUS TEAEs

Serious TEAEs are those events recorded as "Serious Event" on the Adverse Event page of the eCRF. A summary of serious TEAEs by SOC and PT will be prepared.

19.1.6. TEAEs LEADING TO DEATH

TEAEs leading to Death are those events which are recorded as "Fatal" in "Outcome of Adverse Event" on the Adverse Event page of the eCRF. A summary of TEAEs leading to death by SOC and PT will be prepared.

19.1.7. TEAEs OF SPECIAL INTEREST

The following Standardized MedDRA Queries (SMQ) is defined as the Special Interest for this study:

- Hypersensitivity - SMQ Hypersensitivity, SMQ Angioedema, SMQ Anaphylactic reaction
- SMQ Acute Pancreatitis
- SMQ Embolic and thrombotic events

TEAEs of special interest will be summarized by AE of special interest category (Hypersensitivity, Acute Pancreatitis, Embolic and thrombotic events), SOC and PT.

19.1.8. TEAEs BY TREATMENT PHASE

Treatment phase are classified as following:

Treatment Phase in Analysis	Phase Start	Phase End
Remission induction therapy (I_A2, I_A4)	Earliest date of treatment with Vincristine (VCR) or Daunorubicin (DNR) during Remi ion induction therapy	Day before start date of next phase. If subjects discontinue in this phase, EOS (End of study) should be Phase End.
Early consolidation therapy (I_B, I_B+L)	Earliest date of treatment with CPA or 6-MP during Early consolidation therapy	Day before start date of next phase If subjects discontinue in this phase, EOS (End of study) should be Phase End.
Consolidation therapy (M2, M5, HR1/HR2/HR3)	Earliest date of treatment with 6-MP during Consolidation therapy	Day before start date of next phase If subjects discontinue in this phase, EOS (End of study) should be Phase End.
Re-induction therapy (III, III+L) and Interim maintenance therapy (IM)	Earliest date of treatment with DEX, VCR or	EOS (End of study)

	Pirarubicin hydrochloride (THP) during Re-induction therapy	

A subject with a TEAE that occurs in more than one treatment phase is counted in all the phases that the TEAE occurs. For each phase, a subject with multiple occurrences of TEAE within SOC or PT will be counted only once in that SOC or PT.
When calculating percentages for each phase, the number of subjects at risk (ie, subjects who have start date of the phase based on the definition above) will be used as the denominator.

19.1.9. TEAEs WITH CTCAE GRADE 3 OR MORE

A summary of TEAEs with CTCAE grade 3 or more by SOC and PT will be prepared.

19.1.10. SUBGROUP ANALYSIS

The analyses described in Section 19.1.1 through Section 19.1.9 will be presented for subgroups (See Section 8.4).

19.2. SHP674 TEAEs

The analyses described in Section 19.1.1 through Section 19.1.9 will be presented for SHP674 TEAEs.

19.3. TOLERABILITY ASSESMENT

The tolerability assessment period is defined as the period from the pre-treatment phase through remission induction therapy (Day 1 to Day 37).

The analyses described in Section 19.1.1 through Section 19.1.7 and Section 19.1.9 will be presented for TEAEs during the tolerability assessment period (start date of TEAEs falls on Day 12 to Day 37) in part 1.
TEAE during tolerability assessment period will be identified by using “Yes” or “No” of “Intolerable Toxicity?” from the Adverse Event page of the eCRF.
In addition, intolerable toxicity during the tolerability assessment period will be listed.
The details of tolerability assessment in Part 1 is described in Section 7.5 of the protocol.

19.4. DEATHS

If any subjects die during the study, the information will be presented in a summary table and a data listing.
Deaths will be identified by using "Die?" from the Survival Follow-up page of the eCRF.

19.5. LABORATORY EVALUATIONS

Results from the local laboratories will be included in the reporting of this study for hematology, chemistry, coagulation and urinalysis. A list of laboratory assessments to be included in the outputs is included in Section 8.8, 8.9, 8.10, and 8.13 of the protocol.
SI units will be used for presentations.
Quantitative laboratory measurements reported as "< X" (or "<= X"), i.e. below (or at) the lower limit of quantification (BLQ), or "> X" (or ">= X"), i.e. above (or at) the upper limit of quantification (ULQ), will be converted to X for the purpose of quantitative summaries, but will be presented as recorded, i.e. as "< X", "<= X", "> X" or ">= X" in the listings.
The following summaries will be provided for laboratory data:

- Observed values and change from baseline by visit for quantitative measurements
- Shifts from baseline to post-baseline by visit for categorical measurements

All figures of laboratory data, except categorical data, will be presented by each part.
In the case where the results of ALP and LDH are reported by two methods (International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) method and Japan Society of Clinical Chemistry (JSCC) method), the following unified value of ALP/LDH will be defined [1]. The unified value will be used in the analysis and the original value will be included in the listing.

- ALP
    - In case of measurement by IFCC: no need to convert.
    - In case of measurement by JSCC: 0.35 * Value of JSCC method
- LDH
    - In case of measurement by IFCC: no need to convert.
    - In case of measurement by JSCC: 1.0 * Value of JSCC method

19.6. ECG EVALUATIONS

Results from investigational sites will be included in the reporting of this study.
The following ECG (Electrocardiogram) parameters, measured 3 consecutive times, will be reported for this study:

- << Quantitative measurements >>
- Heart Rate (beats/min)
- PR Interval (msec)
- QRS Duration (msec)
- QT Interval (msec)
- QTcF Interval (msec)
- QTcB Interval (msec)
- << Categorical measurements >>
- Interpretation
    - Normal or Abnormal, Not Clinically Significant (NCS)
    - Abnormal, Clinically Significant (CS)

For triplicate assessments, the average of results will be used.
The following summaries will be provided for ECG data:

- Observed values and changes from baseline by visit (refer to Section 8.15 of the protocol) for quantitative measurements
- Shifts from baseline to post-baseline by visit for categorical measurements

All figures of ECG parameters, except interpretation, will be presented by each part.

19.7. VITAL SIGNS

The following Vital Signs measurements will be reported for this study:

- Temperature (C)
- Systolic Blood Pressure (mmHg)
- Diastolic Blood Pressure (mmHg)
- Pulse Rate (beats/min)
- Height (cm)
- Weight (kg)

- SpO_2 (%)
- BSA (m^2)

The following summaries will be provided for vital sign data:

- Observed values and change from baseline by visit (refer to Section 8.6 and 8.7 of the protocol)

All figures of vital signs will be presented by each part.

19.8. ECOG PS

Eastern Cooperative Oncology Group Performance Status (ECOG PS) scores will be reported for this study.
Following summary will be provided:

- Shift from baseline to post-baseline for ECOG PS score by visit (refer to Section 8.6 of the protocol)

19.9. LEFT VENTRICULAR EJECTION FRACTION (LVEF)

LVEF determined by echocardiography scan will be reported for this study.
Following summary will be provided:

- Observed values and change from baseline by visit (refer to Section 8.16 of the protocol)

19.10. IMMUNOLOGICAL TEST

The following Immunology measurements will be reported for this study:

- Immunoglobulin G (IgG)
- Immunoglobulin A (IgA)
- Immunoglobulin M (IgM)

Immunology results will be listed.

20. IMMUNOGENICITY ANALYSIS

All outputs for immunogenicity analysis will be based on the IMAS.

20.1. HANDLING OF MISSING DATA

If the pre-dose sample at induction is missing, the baseline sample status will be considered negative.

20.2. VARIABLE & DERIVATION

The seroconversion is defined as the following two cases:

1. Samples that were negative at baseline and turned positive after treatment
2. The titers of baseline positive samples increased more than 4-fold after treatment

20.3. ANALYSIS

The number and percentage of subjects with positive ADA and anti- PEG antibodies at baseline to the total number of subjects that have samples will be calculated. If a confirmed positive sample at baseline has titer increase after treatment by more than 4-fold, then it will be included within the seroconverters. Persistence of anti-drug or anti-PEG antibodies will be evaluated based on consecutive results after treatment.
The number and percentage of subjects with seroconversions upon treatment will be presented.
Any associations between antibodies and PK will be investigated on a case-by-case basis.
In addition, a subject listing of individual ADA results for each subject and ADA summary table will be provided.

21. PHARMACOKINETICS ANALYSIS

All PK individual listings will include data for all subjects in the SAF; summaries and figures for PK analysis will be based on the PKAS. Subjects will be classified according to Part and BSA dosing cutoff.

21.1. PLASMA ASPARAGINASE ACTIVITY

Subjects with partial asparaginase activity data or protocol deviations or events with the potential to affect PK will be evaluated on a case-by-case basis to determine if sufficient data are available for reliable summarization of asparaginase activity and estimation of PK parameters.
A listing of PK blood sample collection times as well as derived sampling time deviations will be provided. A subject listing of all asparaginase activity-time data for each treatment will be presented.
The asparaginase activity will be summarized for each sampling point using descriptive statistics for each Part

separately, for Part 1 and Part 2 combined (subjects receiving the same dose), and by BSA dosing cutoff. Additional summaries of asparaginase activity will be presented by positive or negative ADA status. Asparaginase activities that are BLQ will be treated as a numeric value of zero for calculation of descriptive statistics. Asparaginase activities that are missing will be omitted from the calculation of descriptive statistics. Abnormal asparaginase activity results (for example, anomalous pre-dose concentration value >5% of C_{max} in the profile in the remission dose, or a quantifiable asparaginase activity after consecutive BLQ results in the terminal phase) will be excluded from the concentration summaries. The entire profile following a pre-dose concentration value >5% of C_{max} will be excluded from descriptive statistics. Descriptive statistic values (minimum, median, maximum, and means) that are BLQ will be presented as 0.

Figures of arithmetic mean asparaginase activity-time data (±SD, as appropriate) will be presented by Part separately, for Part 1 and Part 2 combined (subjects receiving the same dose), and BSA dosing cutoff on linear and semi-logarithmic scales with all active treatments displayed in the same figure.

Individual by-subject asparaginase activity-time data will be generated and presented by treatment on linear and semi-logarithmic scales.

21.2. PHARMACOKINETIC PARAMETERS

Pharmacokinetic parameters for asparaginase activity will be estimated by noncompartmental methods using actual elapsed time from the start of the respective dose administration.

For PK parameter calculations, pre-dose samples that are BLQ or missing will be assigned a numerical value of zero. Any other BLQ value will be assigned a value of zero if they precede quantifiable samples in the initial portion of the profile. A BLQ value that occurs between quantifiable data points, especially prior to C_{max}, will be evaluated to determine if an assigned value of zero makes sense, or if exclusion of the data (flagged in the data and identified to be treated as missing) is warranted. Following C_{max}, BLQ values embedded between 2 quantifiable data points will be treated as missing when calculating PK parameters. If a BLQ value occurs at the end of the collection interval (after the last quantifiable activity), it will be set to zero. If consecutive BLQ values are followed by quantifiable values in the terminal portion of the activity curve, these quantified values will be excluded from the PK analysis by setting them to missing, unless otherwise warranted by the activity-time profile.

Pharmacokinetic parameters to be calculated for asparaginase activity after the remission induction therapy dose of SHP674 will include, but may not be limited to the following, as appropriate:

C_{max}	Maximum asparaginase activity in the sampled matrix, obtained directly from the observed data.
t_{max}	Time of maximum asparaginase activity (h), obtained directly from the observed data.

AUC_{0-t}	Area under the asparaginase activity-time curve in the sampled matrix from zero (pre-dose) to time of last quantifiable asparaginase activity at time "t".
AUC_{0-inf}	Area under the asparaginase activity-time curve in the sampled matrix from zero (pre-dose) extrapolated to infinite time, and extrapolated to infinity by addition of the last quantifiable activity divided by the elimination rate constant: $AUC_{0-t} + C_{last}/\lambda_z$.
λ_z	Apparent terminal rate constant (1/h), determined by linear regression of the terminal points of the log-linear asparaginase activity-time curve. The Best Fit method utilized by WinNonlin will be used to identify the terminal linear phase of the concentration-time profile, with visual assessment and adjustment of the selected data points by the PK scientist if warranted. A minimum of 3 data points after t_{max} will be used for determination.
$t_{1/2}$	Terminal elimination half-life (h), determined as $\ln(2)/\lambda_z$.
CL	Systemic clearance after intravenous dosing, calculated as dose divided by AUC_{0-inf}.
V_{ss}	Estimate of the volume of distribution at steady state following intravenous dosing, calculated as mean residence time extrapolated to infinity (MRTINF)*CL.

The following PK parameters will be calculated for diagnostic purposes and listed, but will not be summarized.

$t_{1/2}$, Interval	The time interval (h) of the log-linear regression to determine λ_z.
$t_{1/2}$, N	Number of data points included in the log-linear regression analysis to determine λ_z. A minimum of 3 data points will be used for determination.
Rsq adjusted	Goodness-of-fit statistic for calculation of λ_z (Coefficient of determination). A value of >= 0.800 for the adjusted R-squared value will be used as the criteria for the reliable estimation of λ_z and reporting of the $t_{1/2}$. If the adjusted R-squared value does not meet this criterion for a given subject, $t_{1/2}$, AUC_{0-inf}, CL, and V_{ss} will be listed but not included in the descriptive statistics.
$\%AUC_{ex}$	Percentage of AUC_{0-inf} obtained by extrapolation, calculated as $[(C_{last}/\lambda_z)/AUC_{0-inf} \times 100]$. If the $\%AUC_{ex}$ is greater than 20% of AUC_{0-inf}, then AUC_{0-inf}, CL, and V_{ss} will be listed but not included in descriptive statistics.

Note: No dose adjustment calculations, e.g., molecular conversions between administered drug product and analyte

measure (e.g., free base or free acid of drug, etc.), should be necessary.
All area under the curve parameters will be calculated using Linear up/Log down trapezoidal summation.
A subject listing of individual PK parameters for each subject will be provided. Pharmacokinetic parameters will be summarized by Part separately, for Part 1 and Part 2 combined (subjects receiving the same dose), and BSA dosing cutoff, as appropriate, using descriptive statistics. Additional summaries of PK parameters will be presented by positive or negative ADA and anti-PEG status. Geometric mean and geometric CV% will not be calculated for t_{max}.
Scatter plots of individual and mean PK parameters versus part will be presented.
Additional parameters (e.g., dose-normalized C_{max}, AUC_{0-t}, and AUC_{0-inf} for SHP674) or graphical presentations of PK data may be added at the discretion of the PK scientist, if appropriate.

22. DATA NOT SUMMARIZED OR PRESENTED

The other variables and/or domains not summarized or presented are:

- Pregnancy test
- Cerebrospinal fluid examination
- CT, MRI and PET
- Viral test

These items excluding the viral test will not be summarized or presented, but will be available in the clinical study database, SDTM and/or ADaM datasets. Viral test results will not be summarized or presented, and not will be collected in the clinical study database.

23. REFERENCES

[1] 前川 真人 (2020). ALP・LD の測定法変更を行うにあたってのご連絡とお願い. 一般社団法人 日本臨床化学会. URL: http://jscc-jp.gr.jp/file/2019/alpld6.pdf

APPENDIX 1. OTHER ASPARAGINASE

The asparaginase other than SHP674 used to define the TEAEs are as follows:

- Leunase
- Erwinase
- Oncasper

APPENDIX 2. PROGRAMMING CONVENTIONS FOR OUTPUTS

IQVIA Output Conventions

Outputs will be presented according to the following.

Univariate Statistics:
See Section 7.7.

Frequencies and percentages (%):

- Frequencies and percentages (%) should be reported to one decimal place as "(99.9 %) ".

Dates & Times

Depending on data available, dates and times will take the form yyyy-mm-ddThh:mm:ss.

Presentation of Part of Study

For outputs, part of study will be represented as follows:

Part of Study	For Tables, Listings and Figures
Part 1	Part 1
Part 2	Part 2
Overall (the combination of Part 1 and 2)	Overall

Listings

All listings will be ordered by the following (unless otherwise indicated in the template):

- Part of Study
- center-subject ID
- start/assessment date and time (where applicable)

APPENDIX 3. FIRST ANALYSIS DATA CUT-OFF PLAN

Introductions

This appendix describes algorithm of data cut-off for SHP674-201 first analysis.
The data cut will be performed programmatically by IQVIA Biostatistics with the raw data transferred by IQVIA data management.

Target subjects and cut-off date for first analysis

All subject reported in the raw data will be included in SDTM.
The cutoff date is in subject-level, the detail derivation is as below:

For **[screening failure]** subject, there is no cut-off. All data will be included.
For other subject, if there is [transition to IB], set the cutoff date as [1 day before the earliest date of 6-MP or CPA administration] or [last administration date of PSL in remission induction therapy], whichever comes later; if there is [no transition to IB], set the cutoff date as [date of discontinuation] or [End of Study Date], whichever comes later.

The programming logic definition is as below:

[screening failure]: The value of "Was the subject enrolled" in "Enrollment" form is "No" (DS_ENR.ENROLL_DSTERM_STD="N")

[transition to IB]: The value of "Will the subject continue to the next phase?" at "Remission Induction Therapy" phase in "Continue to the next phase" is "Yes" (DS_CONT.DSCONT_STD="Yes" when FOLDERNAME="Remission Induction Therapy")

[no transition to IB]: The value of "Will the subject continue to the next phase?" at "Remission Induction Therapy" phase in "Continue to the next phase" is "No" (DS_CONT.DSCONT_SDT="No" when FOLDERNAME="Remission Induction Therapy")

[1 day before the earliest date of 6-MP or CPA administration]: The earliest date of 6-MP or CPA administration start date minus 1 (Select the earliest of EC_6MP.ECSTDAT_RAW and EC_CPA.ECSTDAT_RAW, and then minus 1)
If a waiting period exists, add it to the above.

[date of discontinuation]: The value of "Date of Discontinuation (yyyy/mm/dd)" in "End of Study" form (DS.DISC_DSSTDAT_RAW)

[last administration date of PSL in remission induction therapy]: Select the latest date of Raw.EC_PSL.ECSTDAT_RAW or ECENDAT_RAW when FOLDERNAME="Remission Induction Therapy"

[End of Study Date]: The value of "End of Study Date (yyyy/mm/dd)" in "End of Study" form (DS.DSSTDAT_RAW)

Dataset Requirements

Data cut off will be applied at record level before generating SDTM. As a general principle, the assessment dates that are on or prior to the cutoff date will be kept in SDTM. Handling of records not associated with an assessment date will be explained in details in what follows.

If the date associated to a log form (e.g., Adverse Event form) is partial, i.e., day is missing or day and month are missing, when the available part of the partial date is the same as the cutoff date, this data will not be cut. More specifically, if the day is missing and month and year are the same as the month and year of the data cutoff date, the corresponding data will not be cut. Similarly, if the day and month are missing and the year is the same as the year of data cutoff date, the data will not be cut.

The detailed algorithm for cut-off is provided per dataset type.
There are 6 types of datasets;

1) Demographic and Baseline data
2) Log forms
3) Visit based forms

4) Protocol Deviation
5) Data not submitted to SDTM
6) External data

Detailed algorithm for Cut-Off

1) Demographic and Baseline data.

All data will be included and there will be no cut implemented.

CRF Form	Dataset name
Demographics	DM
Demographics (only enrolled subjects)	DM_2
Enrollment	DS_ENR
Subject Number	SUBN
Medical History	MH

2) Log forms

Data can be cut using the cutoff date based on the date of the event.

The event date will be used to implement the cut (See date/time variable in the table below). If there are event start date and end date, only the start date will be used to implement the cut.

CRF Form	Dataset name	Date/Time Variable	Other condition
Adverse Event	AE	AESTDAT_RAW	
Concomitant Medications (oth r than tudy tr atm nt)	CM	CMSTDAT_RAW	If CMPRIOR="Yes", keep these r cord
End of Study	DS	DSSTDAT_RAW	
Survival Follow-up	DS_SS	SURVFU_DSSTDAT_RAW, LASTCONF_DSSTDAT_RAW, CMSTDAT_RAW, RELAPSE_DSSTDAT_RAW, SECOMALI_DSSTDAT_RAW, DTHDAT_RAW	If all the 6 date variables are after cutoff date, then delete the record; Else if any one of the variables is after cutoff date, then keep the record, but set the date(s) which is(are) after cutoff date to null
Exposure (SHP674)	EC	ECSTDAT_RAW	
Exposure (6-MP)	EC_6MP	ECSTDAT_RAW	
Exposure (Ara-C)	EC_ARAC	ECSTDAT_RAW	
Exposure (CPA)	EC_CPA	ECSTDAT_RAW	
Exposure (DEX)	EC_DEX	ECSTDAT_RAW	

Exposure (DNR)	EC_DNR	ECSTDAT_RAW	
Exposure (IFO)	EC_IFO	ECSTDAT_RAW	
Blood MTX Concentration and Exposure (LV) (M2/M5)	EC_LV	PCDAT_RAW, ECSTDAT_RAW	If both date variables are after cutoff date, then delete the record; Else if any one of the variables is after cutoff date, then keep the record, but set the date(s) which is(are) after cutoff date to null
Blood MTX Concentration and Exposure (LV) (HR2/HR1)	EC_LV_2	PCDAT_RAW, ECSTDAT_RAW	If both date variables are after cutoff date, then delete the record; Else if any one of the variables is after cutoff date, then keep the record, but set the date(s) which is(are) after cutoff date to null
Exposure (MTX) (Pre-treatment Phase)	EC_MTX_1	ECSTDAT_RAW	
Exposure (HD-MTX)	EC_MTX_2	ECSTDAT_RAW	
Exposure (MTX) (Interim Maintenance Therapy)	EC_MTX_3	ECSTDAT_RAW	
Exposure (PSL) (Pre-treatment Phase, Remission Induction Therapy)	EC_PSL	ECSTDAT_RAW	
Exposure (THP)	EC_THP	ECSTDAT_RAW	
Exposure (TIT)	EC_TIT	ECSTDAT_RAW	
Exposure (VCR)	EC_VCR	ECSTDAT_RAW	
Exposure (VDS)	EC_VDS	ECSTDAT_RAW	
Exposure (VP-16)	EC_VP16	ECSTDAT_RAW	
Concomitant Therapies	PR	PRSTDAT_RAW	If PRPRIOR="Yes", keep these records

3) Visit based forms

For visit based forms in which a date of assessment or date of collection is collected, data can be cut based on Target VISIT for scheduled visit. All record reported up to the target VISIT will be included in SDTM.

For unscheduled visit assessment, the cutoff date will be used to implement the cut. For those visit based forms with no date of assessment/date of collection, the date of visit will be used to cut the records. Visit date will be obtained from dataset F_VISIT in such case.

CRF Form	Dataset name	Date/Time Variable	Other condition
Echocardiography	CV	CVDAT_RAW	
ECG Test Results	EG	EGDAT_RAW	

ECG Test Results (Remission Induction Therapy)	EG_LOG	EGDAT_RAW & EGTIM	
Inclusion/Exclusion Criteria	IE	IEDAT_RAW	
ADA	LB_ADA	LBDAT_RAW & LBTIM	
ADA (Remission Induction Therapy)	LB_ADA_LOG	LBDAT_RAW & LBTIM	
Bone Marrow Examination	LB_BM	LBDAT_RAW	
Cerebrospinal Fluid Examination	LB_CF	LBDAT_RAW	
Chemistry	LB_CH	LBDAT_RAW	
Coagulation	LB_CO	LBDAT_RAW	
Pregnancy Test	LB_HCG	LBDAT_RAW	
Hematology	LB_HM	LBDAT_RAW	
Immunology	LB_IM	LBDAT_RAW	
Urinalysis	LB_UR	LBDAT_RAW	
Primary Disease	MH_PD	MHSTDAT_RAW, NCICLAS_RSDAT_RAW, KMT2AAFF_PFDAT_RAW, HYPODIPL_PFDAT_RAW	If all the 4 date variables are after cutoff date, then delete the record; Else if any one of the variables is after cutoff date, then keep the record, but set the date(s) which is(are) after cutoff date to null
CT, MRI and PET	MO	MODAT_RAW	
Plasma Asparaginase Activity	PC	PCDAT_RAW & PCTIM	
Plasma Asparaginase Activity (Remission Induction Therapy)	PC_LOG_1	PCDAT_RAW & PCTIM	
Plasma Asparaginase Activity (Re-induction Therapy)	PC_LOG_2	PCDAT_RAW & PCTIM	
Genetic Testing	PF	PFDAT_RAW	

ECOG Performance Status	QS_ECOG	QSDAT_RAW	
[redacted]			
Risk Classification	RS_RC	RISKCLAS_RSDAT_RAW	
Response to PSL	RS_RP	RESTPSL_RSDAT_RAW	
Unscheduled Assessments	UA	VISDAT_RAW	
Vital Signs	VS	VSDAT_RAW	
Height and Weight	VS_HW	HEIGHT_VSDAT_RAW, WEIGHT_VSDAT_RAW	If both date variables are after cutoff date, then delete the record; Else if any one of the variables is after cutoff date, then keep the record, but set the date(s) which is(are) after cutoff date to null
SpO2	VS_OX	VSDAT_RAW	

4) Protocol Deviation

The source file of protocol deviation is "PD list_yyyymmdd.xlsx". Import the xlsx file and implement the data cut based on the Column I ("発生日"), then export the SAS dataset named SHP674201_PD.

5) Data not submitted to SDTM

Following data does not need any handling, it will not be submitted in SDTM.

CRF Form	Dataset name
Questionnaire of Common Forms	QCOM

6) External data

External data includes Integrated Lab result data (CDM.LAB), ADA result data (CDM. SHP674201_ADA), and PK result data (CDM. SHP674201_PK), no cutoff handling will be performed for these dataset.

- The result which are after cutoff date will be excluded automatically by merging with CRF data in SDTM programming process.

Electronic Signature Manifestation

This page is a manifestation of the electronic signature(s) used in compliance with the organization's electronic signature policies and procedures.

Signer Full Name	Meaning of Signature	Date and Time
[redacted]	Document Approval (I certify that I have the education, training and experience to perform this task)	04 Apr 2021 02:56:54 UTC
	Document Approval (I certify that I have the education, training and experience to perform this task)	04 Apr 2021 23:21:24 UTC
	Document Approval (I certify that I have the education, training and experience to perform this task)	04 Apr 2021 23:28:48 UTC
	Document Approval (I certify that I have the education, training and experience to perform this task)	04 Apr 2021 23:42:43 UTC
	Document Approval (I certify that I have the education, training and experience to perform this task)	05 Apr 2021 01:16:27 UTC
	Document Approval (I certify that I have the education, training and experience to perform this task)	05 Apr 2021 02:06:10 UTC
	Document Approval (I certify that I have the education, training and experience to perform this task)	05 Apr 2021 02:59:08 UTC
	Document Approval (I certify that I have the education, training and experience to perform this task)	05 Apr 2021 11:56:38 UTC