2.0 SYNOPSIS

Name of Customer/Company: Institut de Recherches Internationales Servier (IRIS)

Name of Finished Product: SHP674

Name of Active Ingredient: pegaspargase

Title of Study:

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

Investigators:

Eight investigators at investigative sites that consented at least 1 participant.

Investigative Sites:

Eight investigative sites in Japan consented at least 1 participant.

Publication (Reference):

None

Study Period:	**Phase of Development:**
17-Oct-2019 (Date first participant signed informed consent) – 04-Feb-2022 (Date of last participant completed)	Phase 2

Background and Rationale for the Study:

The treatment of acute lymphoblastic leukemia (ALL) includes long-term use of multiagent chemotherapy. Asparagine is a nonessential amino acid for normal cell growth but is considered essential for leukemia cells as these cells are dependent on exogenous sources of asparagine for survival. Asparaginase selectively kills leukemic cells by depleting asparagine levels. SHP674 is a pegylated formulation of native L-asparaginase with polyethylene glycol (PEG). Pegylation of *Escherichia coli* L-asparaginase used with SHP674 extends circulation time of the enzyme, diminishes immunogenicity, and can be administered to patients who are allergic to native L-asparaginase. In addition, the extension of the plasma half-life of SHP674 allows an administration every 14 days (less frequent than native L-asparaginase). Thus, SHP674 is expected to reduce the burden for patients and health care workers as it requires considerably lower number of doses during remission induction therapy and consolidation therapy. A Phase 2 clinical study consisting of Part 1 (Dose Confirmation) to evaluate the tolerability of SHP674 in Japanese patients and Part 2 to evaluate the efficacy of SHP674 was designed to support the marketing approval of SHP674 in Japan as a first-line treatment for ALL.

Objectives:

<u>Primary Objective:</u>

Part 1

- To assess the tolerability and safety of a single dose of SHP674 in subjects with newly diagnosed, untreated ALL in the tolerability assessment period

Part 2

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

<u>Secondary Objectives:</u>

Part 1

- To assess the percentage of subjects with newly diagnosed, untreated ALL who had 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 pharmacokinetics (PK) of SHP674
- To assess the immunogenicity of SHP674
- To assess the survival rate at 1 year after the start of study treatment

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- To assess the event-free survival rate at 1 year after the start of study treatment

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

Exploratory Objective:

Part 1 and Part 2

- To assess the complete remission (CR) rate, complete remission with incomplete blood count recovery (CRi) rate, and overall response rate (ORR) at the end of remission induction therapy and early consolidation therapy

Study Design:

This was a multicenter, non-randomized, open-label, Phase 2 clinical study of SHP674 in Japanese subjects with newly diagnosed, untreated ALL. The study consisted of Part 1 and Part 2. In Part 1, the tolerability and safety of a single dose of SHP674 were assessed during the tolerability assessment period. The efficacy, safety, and PK of SHP674 at the dose shown to be tolerated in Part 1 were evaluated in Part 2.

The treatment period consisted 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.

Subjects who were newly diagnosed with ALL were stratified into the standard risk (SR), intermediate risk (IR), or high risk (HR) group according to the risk classification criteria based on the comprehensive assessment from the pre-treatment phase through remission induction therapy. Subjects categorized as SR or IR were to receive total 3 doses of SHP674 and those categorized as HR were to receive total 8 doses of SHP674 during the tolerability assessment period (Part 1 only) and the treatment period (Part 1 and Part 2).

Number of Subjects (Planned and Analyzed):

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

Analyzed:
All enrolled set (ENR): 28 subjects (Part 1: 3 subjects, Part 2: 25 subjects)
Safety analysis set (SAF): 26 subjects (Part 1: 3 subjects, Part 2: 23 subjects)
Full analysis set (FAS): 23 subjects (Part 2: 23 subjects)
Immunogenicity analysis set: 25 subjects (Part 1: 3 subjects, Part 2: 22 subjects)
PK analysis set: 26 subjects (Part 1: 3 subjects, Part 2: 23 subjects)

Diagnosis and Main Criteria for Inclusion and Exclusion:

Subjects were included if all of the following inclusion criteria were fulfilled:

1. For Part 1, personally provided informed assent or written informed consent. If informed assent was obtained from a subject, written informed consent was obtained from a legally acceptable representative. For Part 2, written informed consent provided by the subject and/or a legally acceptable representative. Written or verbal assent was obtained from the subject as far as possible even if written informed consent was obtained from a legally acceptable representative;
2. Age 1 to ≤21 years at the time of informed consent;
3. Eastern Cooperative Oncology Group performance status (ECOG PS) 0 to 2;
4. Newly diagnosed, untreated precursor B-cell ALL;
5. No prior therapy for malignant tumor such as chemotherapy and radiation therapy before signing the informed consent;
6. The following laboratory criteria were met at the time of screening:
   - AST and ALT ≤10 × age-specific upper limit of normal (ULN)

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- D-Bil <1.5 mg/dL
- Serum creatinine ≤1.5 × age-specific ULN
- Corrected serum calcium ≤11.5 mg/dL
- Left ventricular ejection fraction (LVEF) ≥63%
- SpO_2 ≥94%
- QT interval corrected by the Fridericia formula ($QTcF = QT/PR^{1/3}$) <0.45 seconds

7. Life expectancy of at least 6 months from the date of enrollment;
8. Women of childbearing potential and fertile men had to agree to use highly effective contraceptive methods from the time of informed consent to at least 6 months after the last dose of SHP674 (for women) or from the start of SHP674 administration to at least 6 months after the last dose of SHP674 (for men). Women of childbearing potential had to have a negative serum or urinary pregnancy test result at screening test.

Subjects were excluded from the study for any of the following reasons:

1. Down syndrome;
2. Mature B-cell ALL (e.g., Burkitt's ALL);
3. Currently active infection;
4. Poorly controlled concurrent illness;
5. Preexisting known coagulopathy (e.g., hemophilia and known protein S deficiency);
6. History of pancreatitis;
7. Continuous use of corticosteroids (transient use for transfusion reactions and topical or local use for the treatment of diseases other than the primary disease were allowed);
8. Positive for HBs antigen, HCV antibody, or HIV antibody. Subjects who were negative for HBs antigen but positive for HBc antibody and/or HBs antibody underwent an HBV DNA test and were excluded from the study if they were positive for HBV DNA (≥20 IU/mL [1.3 LogIU/mL]);
9. Prior treatment or possible prior treatment with an L-asparaginase preparation;
10. History of sensitivity to PEG or PEG-based drugs;
11. Current symptoms or signs of central nervous system (CNS) involvement (e.g., cranial nerve symptoms such as facial palsy), with CNS disease detected on computed tomography (CT) or magnetic resonance imaging (MRI);
12. Pregnant (or planning to become pregnant in near future) or breastfeeding women (breastfeeding women were excluded from the study even if they stopped their breastfeeding);
13. History of previous malignancy, other concurrent malignancy, or secondary ALL; or
14. Other inadequacy determined by the investigator or subinvestigator.

Test Product, Dose, and Mode of Administration, Batch Number:

SHP674 was a white to off-white lyophilized powder and supplied as a sterile, single-use vial. A vial containing 3750 international unit of L-asparaginase activity (IU) active ingredient. Prior to administration, SHP674 was dissolved in sterile water for injection to make 750 IU/mL of solution and was stored refrigerated at 2ºC to 8ºC.

The intravenous (IV) dose of SHP674 was 2500 IU/m^2 for the subjects with body surface area (BSA) ≥0.6 m^2 or 82.5 IU/kg for the subjects with BSA <0.6 m^2. The backbone therapy drugs for combination chemotherapy other than SHP674 were administered.

Batch numbers:

SHP674: LC001456, LC001572, LC001614, LC001725, LC001820, and LC001862
Backbone therapy drugs: refer to Appendix 16.1.6

Reference Therapy, Dose, and Mode of Administration, Batch Number:

Not applicable

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Duration of Treatment:

Subjects stratified into the SR or IR group: 41 weeks
Subjects stratified into the HR group: 45 weeks

Endpoints:

Primary Endpoint:

Part 1
- Incidence and nature of treatment-emergent adverse events (TEAEs) and SHP674-related TEAEs that occurred or worsened during the tolerability assessment period

Part 2
- Achievement of a plasma asparaginase activity of ≥0.1 IU/mL 14 days (336 hours) after the first dose of SHP674

Secondary Endpoints:

Part 1
- Safety: incidence and nature of TEAEs and drug-related TEAEs, laboratory values, and vital signs
- PK: PK parameters
- Immunogenicity: anti-drug antibody (ADA) (i.e., anti-SHP674 antibody) and anti-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, and event-free survival rate at 1 year after the start of study treatment

Part 2
- Safety: incidence and nature of TEAEs and drug-related TEAEs, laboratory values, and 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, and event-free survival rate at 1 year after the start of study treatment

Exploratory Endpoint:

Part 1 and Part 2
- CR rate, CRi rate, and ORR at the end of remission induction therapy and early consolidation therapy

Statistical Methods:

Efficacy Analysis:

Efficacy analyses for the primary and secondary endpoints were carried out using the FAS. Efficacy analyses for the secondary endpoints was also carried out using the SAF.

The number and percentage of subjects with a plasma asparaginase activity of ≥0.1 IU/mL 14 days (336 hours) after the first dose of SHP674 were calculated. The corresponding 95% confidence intervals (CIs) were calculated based on the Clopper-Pearson method. 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, and the corresponding 95% CIs were calculated.

The overall survival (OS) rate and the event-free survival rate at 1 year (1 year was defined as 365 days) after the first dose of SHP674 were calculated as the Kaplan-Meier estimate and 95% CI for survival function. A summary and a plot of the Kaplan-Meier estimates of the survival function were provided along with the number at risk. The CR rate, CRi rate, and ORR (CR + CRi) at the end of remission induction therapy and early consolidation therapy, and the corresponding 95% CIs were calculated.

Pharmacokinetic Analysis:

Pharmacokinetic analyses were carried out using the PK analysis set. Subjects with partial asparaginase activity data or protocol deviations or events with the potential to affect PK were evaluated on a case-by-case basis to determine if sufficient data were available for reliable summarization of asparaginase activity and estimation of PK parameters.

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A listing of PK blood sample collection times as well as derived sampling time deviations was provided. All asparaginase activity-time data for each treatment were listed.

The asparaginase activity was summarized for each sampling point using descriptive statistics for each Part and body surface area (BSA) dosing cutoff. Additional summaries of asparaginase activity were presented by positive or negative ADA status.

Figures of arithmetic mean asparaginase activity-time data (± standard deviation [SD], as appropriate) were presented by Part and BSA dosing cutoff on linear and semi-logarithmic scales with all active treatments displayed in the same figure.

Pharmacokinetic parameter computations were performed using Phoenix® WinNonlin® 8.3 (Certara L.P., Princeton, New Jersey). Pharmacokinetic parameters for asparaginase activity were estimated by noncompartmental methods using actual elapsed time from the start of the respective dose administration.

A subject listing of individual PK parameters for each subject was provided. Pharmacokinetic parameters were summarized by Part and BSA dosing cutoff, using descriptive statistics. Additional summaries of PK parameters were presented by positive or negative ADA and anti-PEG antibody status. Scatter plots of individual and mean PK parameters versus part were presented.

Safety Analysis:

Safety analyses were carried out using the SAF. All safety analyses were performed separately for Part 1 and Part 2 of the study as well as for the combination of Part 1 and Part 2 resulting in all subjects dosed in the study.

The frequencies of all TEAEs and SHP674-related TEAEs that occurred or worsened after the start of study treatment were summarized by nature of events based on the Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs) and system organ classes (SOCs). For Part 1, the frequencies of all TEAEs and SHP674-related TEAEs that occurred or worsened during the tolerability assessment period were summarized.

The frequencies of TEAEs of special interest ("hypersensitivity", "acute pancreatitis", and "embolic and thrombotic events") were summarized. The frequencies of TEAEs by treatment phase were summarized. For subgroup analyses, TEAEs by age at informed consent and WBC count at baseline visit were assessed.

Descriptive statistics of laboratory parameters, continuous variables of vital signs and echocardiography were calculated for each time point. Shift tables for qualitative urinalysis results, 12-lead ECG data, and ECOG PS scores from baseline to each time point after the start of administration were created.

Persistence of ADAs or anti-PEG antibodies in the immunogenicity analysis set was evaluated based on consecutive results after treatment. The number and percentage of subjects with seroconversions by visit upon treatment were presented.

Summary – Conclusions:

A total of 26 subjects (3 subjects in Part 1 and 23 subjects in Part 2) received at least one dose of SHP674 with the combination of backbone therapy drugs. The IV dose of SHP674 used in Part 2 was the same as the dose in Part 1. The median age was 4.8 years; 19 subjects were under 10 years of age. The number of male and female subjects was equal (13 subjects each).

In the SR/IR group, 22 of 25 subjects received 3 doses of SHP674 as scheduled in the protocol. Two subjects received 1 dose and 1 subject received 2 doses due to treatment discontinuation. For 1 subject in the HR group in which 8 doses of SHP674 were planned to be administered, only 3 doses were administered due to treatment discontinuation.

Activity and Efficacy Results:

- In Part 2, all 23 subjects (100.0%, 95% CI: 85.2%, 100.0%) achieved a plasma asparaginase activity of ≥0.1 IU/mL 14 days after the first dose of SHP674.
- In Part 2, all 23 subjects (100.0%) with evaluable samples had a plasma asparaginase activity of ≥0.1 IU/mL from 5 minutes to 14 days after the first dose of SHP674. One of 22 subjects (4.5%) had a decreased plasma asparaginase activity of <0.1 IU/mL 18 days after the first dose of SHP674.

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- In Part 1, all 3 subjects (100.0%, 95% CI: 29.2%, 100.0%) achieved a plasma asparaginase activity of ≥0.1 IU/mL 14 days after the first dose of SHP674. For each time point, all subjects (100.0%) with evaluable samples had a plasma asparaginase activity of ≥0.1 IU/mL from 5 minutes to 18 days after the first dose of SHP674.
- Both survival rate and event-free survival rate at 1 year after the first dose of SHP674 were 100.0% across Part 1 and Part 2.
- In both Parts, all analyzed subjects (100.0%) achieved CR or CRi at both time points for CR evaluation (at the end of remission induction therapy and early consolidation therapy). ORRs were 100.0% across Part 1 and Part 2.

Pharmacokinetic Results:

- In general, the mean plasma asparaginase activity-time profiles across the 2 dosing regimens based on BSA dosing cutoff (82.5 IU/kg for subjects with a BSA <0.6 m^2 [n = 4] and 2500 IU/m^2 for subjects with a BSA ≥0.6 m^2 [n = 22]) were similar.
- Arithmetic mean SHP674 exposure (maximum observed plasma asparaginase activity [C_{max}]; AUC from time 0 to infinity [AUC_{0-inf}]) was similar following an IV infusion of 82.5 IU/kg for subjects with a BSA [redacted] and 2500 IU/m^2 for subjects with a BSA ≥0.6 m^2 [redacted]
- Arithmetic mean SHP674 exposure (C_{max}; AUC_{0-inf}) was similar following Part 1 [redacted] and Part 2 [redacted]
- Median time to peak observed plasma asparaginase activity (t_{max}) was [redacted] hours and [redacted] hours for the 2500 IU/m^2 and 82.5 IU/kg doses, respectively.
- Arithmetic mean elimination half-life was 121.0 hours (range [min, max] [redacted]) and 92.52 hours (range [min, max] [redacted]) for the 2500 IU/m^2 and 82.5 IU/kg dosing regimens, respectively, with high variability (82.7% CV) observed in the 2500 IU/m^2 dose.
- Arithmetic mean apparent clearance (CL) values were [redacted] following administration of 2500 IU/m^2 (for subjects with a BSA ≥0.6 m^2) and [redacted] following administration of 82.5 IU/kg dose (for subjects with a BSA <0.6 m^2).
- Arithmetic mean volume of distribution at steady state (V_{ss}) values were [redacted] and [redacted] for 2500 IU/m^2 and 82.5 IU/kg doses, respectively.

Safety Results:

- No subject experienced an intolerable toxicity during the tolerability assessment period designed in Part 1.
- All 26 subjects (100.0%) treated in Part 1 and Part 2 experienced at least one TEAE. The most frequently reported TEAEs (≥70% of subjects) of any grade included platelet count decreased (96.2%), anaemia and white blood cell count decreased (92.3% each), vomiting (80.8%), febrile neutropenia and alopecia (76.9% each), and constipation and blood fibrinogen decreased (73.1% each).
- All 26 subjects (100.0%) treated in Part 1 and Part 2 experienced at least one TEAE related to SHP674. The most frequently reported TEAEs related to SHP674 (≥50% of subjects) included blood fibrinogen decreased (73.1%), antithrombin III decreased and white blood cell count decreased (57.7% each), and platelet count decreased (53.8%).
- All 26 subjects (100.0%) treated in Part 1 and Part 2 experienced at least one TEAE of Grade ≥3. The most frequently reported TEAEs of Grade ≥3 (≥50% of subjects) included platelet count decreased (96.2%), anaemia and white blood cell count decreased (92.3% each), febrile neutropenia (76.9%), blood fibrinogen decreased (65.4%), and alanine aminotransferase increased (50.0%).
- The incidences of TEAEs were similar across the 4 therapy periods.
- The most frequently reported TEAEs were consistent between the <10-years-old group and the ≥10-year-old group.
- No deaths were reported. Eleven subjects (42.3%) experienced at least of one serious TEAE each; of which, Grade 1 vomiting and Grade 4 pancreatitis acute were considered related to SHP674.
- Two subjects (7.7%) experienced non-serious TEAEs leading to discontinuation of SHP674; they were Grade 3 anaphylactic reaction and Grade 3 pancreatitis. Both TEAEs were considered related only to SHP674.
- One subject had an accidental overdose of SHP674. No pregnancies were reported during the study.

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- For laboratory measurements, there were no clinically meaningful trends over time in laboratory tests (blood chemistry, hematology, coagulation, and urinalysis).
- There were no clinically meaningful findings in vital signs, ECG interpretations, or any other measurements.
- Seroconversion for ADAs was identified in 2 subjects (8.0%).

Conclusions:

- All 26 subjects treated in Part 1 and Part 2 achieved a plasma asparaginase activity of ≥0.1 IU/mL from 5 minutes to more than 14 days after the first dose of SHP674.
- Both survival rate and event-free survival rate at 1 year after the first dose of SHP674 were 100.0% across Part 1 and Part 2.
- Based on C_{max} and $AUC_{0\text{-}inf}$, SHP674 exposures were similar following an IV infusion of 82.5 IU/kg for subjects with a BSA <0.6 m^2 and 2500 IU/m^2 for subjects with a BSA ≥0.6 m^2. Median t_{max} was independent of the BSA-assigned dose.
- Arithmetic mean elimination half-life was approximately [redacted] for both dosing regimens with higher variability (82.7% CV) observed in the 2500 IU/m^2 dose.
- Arithmetic mean CL and V_{ss} were approximately 2.7-fold higher following an IV infusion of 2500 IU/m^2 for subjects with a BSA ≥0.6 m^2 when compared with an IV infusion of 82.5 IU/kg for subjects with a BSA <0.6 m^2.
- Arithmetic mean SHP674 peak and total exposures were similar for the limited number of subjects with positive ADA or anti-PEG antibody compared to the subjects with negative ADA or anti-PEG antibody status.
- Seroconversion for ADAs was identified in 2 subjects (8.0%).
- No new safety concerns were identified. The safety profile was consistent with the known safety profile of SHP674.

Date and Version of Report:

29-Aug-2022