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

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Protocol

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

Protocol No.:	SHP674-201 (Referred to internally at Servier as CL1-95014-001)
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In-country caretaker	Kyowa Kirin Co., Ltd. 1-9-2, Otemachi, Chiyoda-ku, Tokyo, Japan

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

List of Abbreviations

Abbreviations	Expanded Form
6-MP	6-Mercaptopurine
ADA	Anti-drug antibody
ALL	Acute lymphoblastic leukemia
Ara-C	Cytarabine
BMA	Bone marrow aspiration
CNS	Central nervous system
CPA	Cyclophosphamide
[redacted]	
CRT	Cranial radiotherapy
CSI	Craniospinal irradiation
CTCAE	Common Terminology Criteria for Adverse Events
Cy	Cytoplasmic
DEX	Dexamethasone
DIC	Disseminated intravascular coagulation
DNR	Daunorubicin
FCM	Flow cytometry
FDP	Fibrin/Fibrinogen Degradation Products
G-CSF	Granulocyte colony-stimulating factor
HR	High risk
IFO	Ifosfamide
IR	Intermediate risk
LV	Leucovorin
MRD	Minimal residual disease
MTX	Methotrexate
NCC	Nucleated cells
NUDT15	Nudix Hydrolase 15
[redacted]	
PD	Pharmacodynamics
PEG	Polyethylene glycol
PGR	Prednisolone-good responder
PK	Pharmacokinetics/pharmacokinetic
PPR	Prednisolone-poor responder
PS	Performance status
PSL	Prednisolone
RT-PCR	Reverse transcriptase-polymerase chain reaction
SD	Standard deviation
SR	Standard risk
TEAE	Treatment-emergent adverse event
THP	Pirarubicin hydrochloride
TIT	Triple intrathecal therapy
VCR	Vincristine
VDS	Vindesine
VP-16	Etoposide

Definition of Terms

Term	Definition and Explanation
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
LLT	Lowest level term in MedDRA
MedDRA	ICH Medical Dictionary for Regulatory Activities
PT	Preferred term in MedDRA
SOC	System organ class in MedDRA
Pharmaceuticals and Medical Devices Act	Japanese law to ensure the quality, efficacy, and safety of pharmaceuticals, quasi-drugs, cosmetics, and medical devices.
AUC	Area under the plasma asparaginase activity-time curve
$AUC_{0\text{-}25d}$	Area under the plasma asparaginase activity-time curve from time 0 to 25 days after administration
$AUC_{0\text{-}inf}$	Area under the plasma asparaginase activity-time curve from time 0 to infinity
$AUC_{0\text{-}t}$	Area under the plasma asparaginase activity-time curve from time 0 to t
BFM	Berlin-Frankfurt-Münster
BLA	Biological License Application
CL	Clearance; $CL=Dose/AUC_{0\text{-}inf}$
C_{max}	Maximum observed plasma asparaginase activity in plasma
COG	Children's Oncology Group
ECOG	Eastern Cooperative Oncology Group
GCP	Good Clinical Practice
HBc antibody	Hepatitis B core antibody
HBs antigen	Hepatitis B surface antigen
HBs antibody	Hepatitis B surface antibody
HIV antigen	Human immunodeficiency virus antigen
IUPAC	International Union of Pure and Applied Chemistry
IRB	Institutional Review Board
IU	International unit
JPLSG	Japanese Pediatric Leukemia/Lymphoma Study Group
$t_{1/2}$	Biological half-life
t_{max}	Time to peak plasma asparaginase activity
V_{ss}	Volume of distribution at steady state

List of Parameters (Hematology, Chemistry, Urinalysis, Vital Signs, ECG, and Genetic Testing)

Parameter	Abbreviation	Display Name on Case Report Form
Red blood cell count	RBC	Erythrocytes
White blood cell count	WBC	Leukocytes
Hematocrit	Ht	Hematocrit
Hemoglobin concentration	Hb	Hemoglobin
Platelet count	PLT	Platelets
Basophil count	Baso	Basophils
Eosinophil count	Eosino	Eosinophils
Neutrophil count	Neutro	Neutrophils
Lymphoblast count	–	Lymphoblasts
Monocyte count	Mono	Monocytes
Lymphocyte count	Lymph	Lymphocytes
C-reactive protein	CRP	C-reactive protein

Gamma-glutamyltransferase	γ-GTP	Gamma Glutamyl Transferase
Aspartate aminotransferase	AST	Aspartate Aminotransferase
Amylase	AMY	Amylase
Alanine aminotransferase	ALT	Alanine Aminotransferase
Alkaline phosphatase	ALP	Alkaline Phosphatase
Albumin	ALB	Albumin
Potassium	K	Potassium
Calcium	Ca	Calcium
Creatinine	Cr	Creatinine
Chloride	Cl	Chloride
Blood urea nitrogen	BUN	Urea Nitrogen
Blood glucose	Glu	Glucose
Total cholesterol	T-Cho	Cholesterol
Total bilirubin	T-Bil	Total bilirubin
Total protein	TP	Protein
Triglyceride	TG	Triglycerides
Direct bilirubin	D-Bil	Direct bilirubin
Sodium	Na	Sodium
Lactate dehydrogenase	LDH	Lactate Dehydrogenase
Uric acid	UA	Urate
Corrected serum calcium	Corrected serum Ca	Calcium Corrected
Lipase	–	Lipase
Phosphate	P	Phosphate
Urine occult blood	–	Occult Blood
Urine urobilinogen	–	Urobilinogen
Urine ketone bodies	–	Ketone Bodies
Urine protein	–	Protein
Urine glucose	–	Glucose
Percutaneous arterial oxygen saturation	SpO_2	Percutaneous Arterial Oxygen Saturation
Diastolic blood pressure	–	Diastolic Blood Pressure
Systolic blood pressure	–	Systolic Blood Pressure
Eastern Cooperative Oncology Group Performance Status	ECOG PS	Eastern Cooperative Oncology Group Performance Status
Height	–	Height
Temperature	–	Temperature
Weight	–	Weight
Pulse rate	–	Pulse Rate
D-dimer	–	D-dimer
Antithrombin activity	–	Antithrombin Activity
Activated partial thromboplastin time	APTT	Activated Partial Thromboplastin Time
Fibrinogen	–	Fibrinogen
Fibrin/fibrinogen degradation products	FDP	Fibrin/Fibrinogen Degradation Products
Protein S	–	Protein S
Prothrombin time-international normalized ratio	Prothrombin time -INR	Prothrombin Time-International Normalized Ratio
Immunoglobulin A	IgA	Immunoglobulin A
Immunoglobulin G	IgG	Immunoglobulin G
Immunoglobulin M	IgM	Immunoglobulin M

HBs antigen test	−	HBs antigen test
HBs antibody test	−	HBs antibody test
HBc antibody test		HBc antibody test
HCV antibody test	−	HCV antibody test
HIV antibody test	−	HIV antibody test
HBV DNA test	−	HBV DNA test
Time from the beginning of the P wave to the beginning of the QRS complex on an electrocardiogram	PR interval	PR Interval
Time from the beginning of the Q wave to the end of the S wave on an electrocardiogram	QRS duration	QRS Duration
Time from the beginning of the Q wave to the end of the T wave on an electrocardiogram	QT interval	QT Interval
QT interval corrected for heart rate using the Bazett formula or QT interval corrected for heart rate using the Fridericia formula	QTc interval (QTcB, QTcF)	QTcB Interval, QTcF Interval
Heart rate	−	Heart Rate
Computed tomography	CT	Computed Tomography
Magnetic resonance imaging	MRI	Magnetic Resonance Imaging
Positron emission tomography	PET	Positron Emission Tomography
Positron Emission Tomography- Computed Tomography	PET-CT	Positron Emission Tomography-Computed Tomography
Bone marrow lymphoblasts	−	Blasts/Nucleated cells
Nucleated cells	−	Nucleated cells
Pregnancy test	−	Pregnancy Test
NUDT15 codon 139 polymorphism analysis	NUDT15	Nudix Hydrolase 15

Study participation period

The study participation period for each subject in this study is defined as the period from the day of informed consent to the day of the last assessment prescribed in the protocol. After the end of the study participation period, subjects will be followed for survival as specified in Section 8.24.

Time points for investigational product administration, observations, and tests

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. Subsequently, the week that is Y weeks after the start of the pre-treatment phase will be regarded as Week Y. The week preceding the start week of the pre-treatment phase is defined as Week 0.

Subject identification code

The investigator or subinvestigator will assign subject identification codes (SIDs) to all subjects who give informed consent at the investigative site according to the following rule:

SID: [redacted]

ex.) The SID of the first subject (Part 1) who provides informed consent at XX Hospital (investigative site code: [redacted]) in Japan is [redacted]

PROTOCOL SYNOPSIS

I Study Title

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

II Study Objectives and Endpoints

Study Objectives

Part 1

- Primary objective
  - 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.
- Secondary objectives
  - 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.

[redacted]

Part 2

- Primary objective
  - 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.
- Secondary objectives
  - 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]

Endpoints

Part 1

- Primary endpoint
  - Incidence and nature of treatment-emergent adverse events (TEAEs) and SHP674-related TEAEs that occur or worsen during the tolerability assessment period.
- Secondary endpoints
  - Safety
    - Incidence and nature of treatment-emergent adverse events (TEAEs) and drug-related TEAEs
    - Laboratory values
    - Vital signs
  - PK
    - PK parameters
  - Immunogenicity
    - ADA (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
    - Event-free survival rate at 1 year after the start of study treatment

[redacted]

Part 2

- Primary endpoint
  - Achievement of a plasma asparaginase activity of ≥0.1 IU/mL 14 days (336 hours) after the first dose of SHP674.
- Secondary endpoints
  - Safety
    - Incidence and nature of treatment-emergent adverse events (TEAEs) and drug-related TEAEs
    - Laboratory values
    - Vital signs
  - PK
    - PK parameters
  - Immunogenicity
    - ADA (anti-SHP674 antibody) 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]

III Study Design

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). The dosing schedule of each drug including SHP674 is outlined in Table 7-1 to Table 7-3.

Part 1

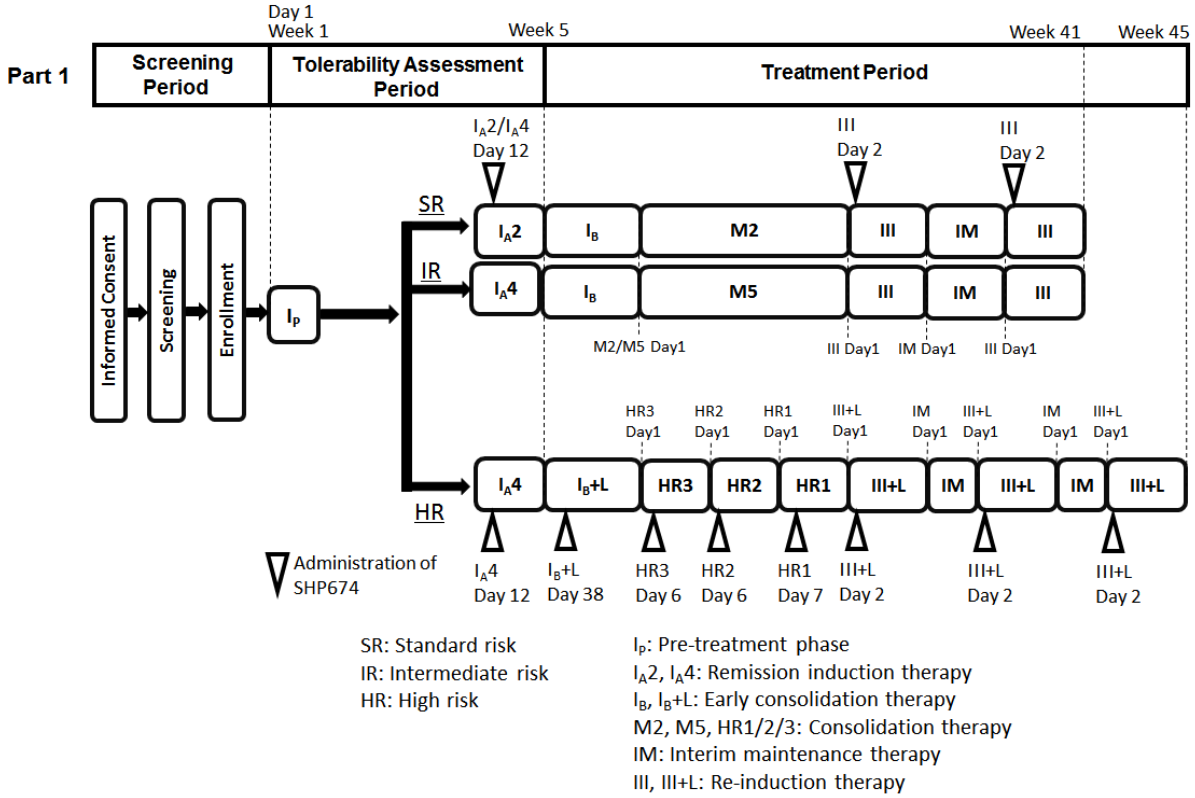
Part 1 is comprised of a screening period and a subsequent tolerability assessment period (from the pre-treatment phase through remission induction therapy [Day 1 to Day 37]; for at least 25 days after the first dose of SHP674) and a treatment period (from early consolidation therapy to the end-of-study assessment). Subjects categorized as SR or IR will receive a total of 3 doses of SHP674 and those categorized as HR will receive a total of 8 doses of SHP674 during the tolerability assessment period and the treatment period. The outline of the study design in Part 1 is shown in the figure below. 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.

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).

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.

Outline of Study Design in Part 1



SR: Standard risk
IR: Intermediate risk
HR: High risk

I_P: Pre-treatment phase
I_A2, I_A4: Remission induction therapy
I_B, I_B+L: Early consolidation therapy
M2, M5, HR1/2/3: Consolidation therapy
IM: Interim maintenance therapy
III, III+L: Re-induction therapy

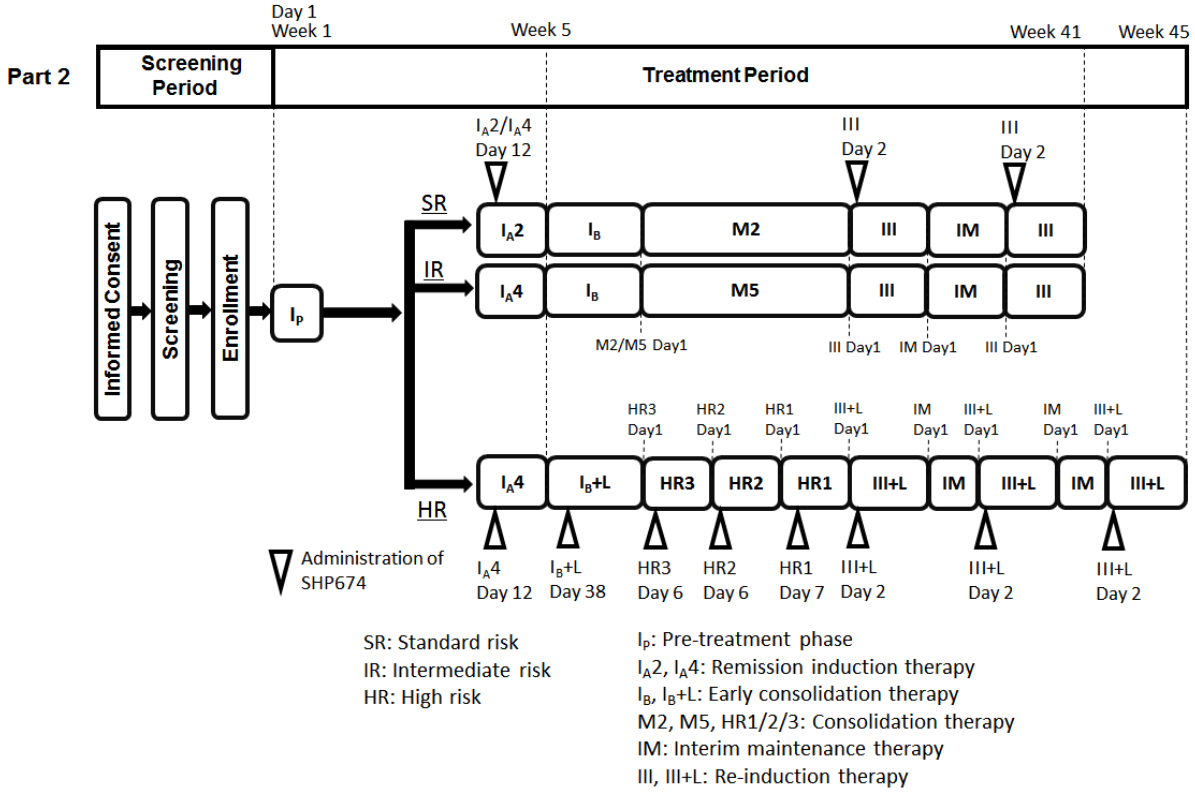
Part 2

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 below. 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.

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 pharmacokinetics of SHP674 at the dose shown to be tolerated in Part 1.

Outline of Study Design in Part 2



IV Target Disease

ALL

V Inclusion Criteria

Subjects who are enrolled in the study must meet all of the following criteria:

1) For Part 1, personally provided informed assent or written informed consent. If informed assent is obtained from a subject, written informed consent should be 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 should be obtained from the subject as far as possible even if written informed consent is 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 (see Attachment 5 to the protocol [supplement]);
5) No prior therapy for malignant tumor such as chemotherapy and radiation therapy before signing the informed consent;
6) The following laboratory criteria are met at the time of screening;
   - AST and ALT ≤10 × age-specific upper limit of normal (ULN)
   - D-Bil <1.5 mg/dL
   - Serum creatinine ≤1.5 × age-specific ULN
   - Corrected serum calcium ≤11.5 mg/dL

- Left ventricular ejection fraction ≥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 must 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 must have a negative serum or urinary pregnancy test result at screening test.

* *Note:*

- *A woman of childbearing potential is defined as a woman who has experienced her first menstruation, has not undergone hysterectomy, bilateral tubal ligation, or bilateral ovariectomy and is not postmenopausal. Postmenopausal status is defined as amenorrhea of ≥12 consecutive months with no specific causes.*

- *Since there is a potential for an indirect interaction between SHP674 and oral contraceptives, the concomitant use of SHP674 and oral contraceptives is not recommended. Another, non-oral contraceptive method should be used in women of childbearing potential.*

VI Exclusion Criteria

Subjects must be excluded from participating in this study if they meet any of the following criteria:

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 will be allowed);
8) Positive for HBs antigen, HCV antibody, or HIV antibody. Subjects who are negative for HBs antigen but positive for HBc antibody and/or HBs antibody will undergo an HBV DNA test and will be excluded from the study if they are 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 polyethylene glycol (PEG) or PEG-based drugs;
11) Current symptoms or signs of CNS involvement (e.g., cranial nerve symptoms such as facial palsy), with CNS disease detected on CT or MRI;
12) Pregnant (or planning to become pregnant in near future) or breastfeeding women (breastfeeding women will be excluded from the study even if they stop their breastfeeding);
13) History of previous malignancy, other concurrent malignancy, or secondary ALL; or
14) Other inadequacy determined by the investigator or subinvestigator.

VII Target Sample Size

Part 1 = 3 to 6 evaluable subjects

Part 2 = 22 subjects

VIII Investigational Products

Test drug

Company code: SHP674

Nonproprietary name: Pegaspargase

Backbone Therapy drugs provided by the Sponsor for investigational use

Predonine® Tablets 5 mg

Company code: PSL-SER-PO-T

Non-proprietary name: Prednisolone

Prednisolone Powder 1%

Company code: PSL-SER-PO-P

Non-proprietary name: Prednisolone

Predonine® 50 mg (water-soluble)

Company code: PSL-SER

Non-proprietary name: Prednisolone sodium succinate

Endoxan® 500 mg (for Injection)

Company code: CPA-SER

Non-proprietary name: Cyclophosphamide hydrate

Leukerin® Powder 10%

Company code: 6-MP-SER

Non-proprietary name: Mercaptopurine hydrate

Lastet® Inj.100 mg/5 mL

Company code: VP-16-SER

Non-proprietary name: Etoposide

Ifomide® 1 g (for injection)

Company code: IFO-SER

Non-proprietary name: Ifosfamide

Decadron® Tablets 0.5 mg/4 mg

Company code: DEX-SER-PO

Non-proprietary name: Dexamethasone

Decadron® Phosphate Injection 6.6 mg

Company code: DEX-SER-IV

Non-proprietary name: Dexamethasone sodium phosphate

Methotrexate® Tablets 2.5 mg

Company code: MTX-SER

Non-proprietary name: Methotrexate

Methotrexate® Injection 1000 mg

Company code: HD-MTX-SER

Non-proprietary name: Methotrexate

X Planned Study Period

May, 2019 to December, 2022

A snapshot of data will be taken for analysis of all available endpoints after all subjects completed remission induction therapy. The clinical study report (CSR) will be based on the data from the period of remission induction phase. Additional safety, PK and survival final analysis of all secondary [redacted] endpoints will be performed after all subjects complete the study (365 [±7] days after the first dose of SHP674 or at the time all subjects complete the study) and submitted as an addendum to the CSR.

Table of Contents

1 INTRODUCTION

1.1 Background

Leukemia is the most common pediatric malignancy. Acute lymphoblastic leukemia (ALL) is the most common type (46.6%) of acute leukemia in childhood.[1,2] About 500 children are newly diagnosed with ALL each year in Japan.[2] When looking at the proportion of patients by age group, approximately 40% of all patients newly diagnosed with pediatric ALL are 1 to 4 years of age, approximately 30% are 5 to 9 years, and approximately 20% are 10 to 14 years. The proportion of patients newly diagnosed with ALL is low at 15 to 19 years, accounting for approximately 4% of all patients newly diagnosed with ALL.[2] According to the immunological classification, precursor B-cell ALL accounts for 85.6% of all pediatric ALL. The male-to-female ratio is 1.34:1; the proportion of male children is slightly larger than that of female children.[3]

Previously, ALL and malignant lymphoma were considered to be derived from bone marrow and lymph nodes, respectively. ALL was diagnosed in the presence of bone marrow infiltration with lymphoblasts, and lymphoblastic lymphoma (LBL) was diagnosed in the absence of bone marrow infiltration. However, according to the WHO classification published from 2008 onwards, lymphoid tumors are broadly divided into B-cell type and T-cell and natural killer-cell (T/NK-cell) type, and ALL and LBL are classified as being derived from precursor B cells and precursor T cells, the most immature type of B and T cells.[4]

ALL and LBL are biologically the same disease, but in general, ALL is diagnosed when extensive tumor cell infiltration is noted in peripheral blood and the percentage of blasts in bone marrow is ≥25%, and LBL is diagnosed when the percentage of blasts is <25%. Thus, in this study, ALL is to be diagnosed when the percentage of lymphoid tumor cells in bone marrow is ≥25%.[5]

In Japan, stratified treatment according to risk groups is recommended for patients with pediatric ALL.[6] Required tests depend on the age of patients. Treatment is stratified based on the presence or absence of rearrangement of the MLL gene for patients <1 year and based on the combination of response to prednisolone (circulating lymphoblast count 8 days after 7-day administration of prednisolone), immunological classification, age, and white blood cell count for patients ≥1 year. Treatment requires the reassessment of risks based on information such as the proportion of bone marrow lymphoblasts and the presence or absence of minimal residual disease after chemotherapy in the course of the treatment. If the proportion of lymphoblasts is ≤1%, minimal residual disease is difficult to detect by microscopy, but can be detected by flow cytometry or polymerase chain reaction. Treatment strategy is recommended to be determined by assessing response to treatment based on the quantitative measurement of minimal residual disease. Remission induction therapy for patients with pediatric ALL was established in 1970's.[7] As it is now, triple combination therapy with prednisolone or dexamethasone, vincristine, and L-asparaginase provides long-term remission in approximately 80% of patients. In addition, intrathecal injection of methotrexate is essential to prevent the onset of central nervous system leukemia.[8] In high risk patients, quadruple combination therapy with the above 3 drugs plus an anthracycline has shown a trend toward further improvement in treatment results.[9] The Practical Guideline for Pediatric Leukemia and Lymphoma (2016 version)[6] recommends that post-remission consolidation therapy be started immediately after the end of remission induction therapy. The Practical Guidelines for Hematological Malignancies, 2018 recommend that adult patients up to about 30 years of age receive treatment per pediatric protocol.[5]

The worldwide standard treatments for pediatric ALL include the treatment backbones established by the Children's Oncology Group (COG) and the Berlin-Frankfurt-Münster (BFM) group. In Japan, there is little experience with the COG backbone, and treatment based on the BFM backbone described above has been adopted.

1.2 Positioning of L-asparaginase Preparations in the Treatment of ALL

The mechanism of action of L-asparaginase is considered to be a selective killing effect on leukemia cells exerted by depleting asparagine in blood. Lymphoblastic leukemia cells cannot produce asparagine by themselves because of low expression of asparagine synthetase; extracellular asparagine is essential for the survival of leukemia cells. L-asparaginase exerts an antitumor effect by hydrolyzing blood asparagine into aspartic acid and ammonia and thereby depleting asparagine in blood. On the other hand, normal cells, having ability to synthesize asparagine, are unlikely to be affected by the depletion of blood asparagine.

Treatment for patients with acute ALL consists of remission induction therapy, early consolidation therapy, central nervous system preventive therapy, consolidation therapy, and maintenance therapy, all of which are combination therapies with antitumor drugs. L-asparaginase is incorporated into combination therapy and plays an important role as a key drug for the treatment of patients with ALL, since it causes relatively mild myelosuppression and has no cross-resistance with other anticancer drugs. However, L-asparaginase is a protein derived from *Escherichia coli*, and some patients have a difficulty in the continued use of the drug due to allergic reactions such as anaphylactic shock, which prevents the patients from completing treatment. Many of the patients with ALL who are allergic to L-asparaginase have a difficulty in continuing treatment and cannot receive chemotherapy of adequate intensity, and this leads to worsening of prognosis in these patients.

1.3 SHP674

SHP674 (international non-proprietary name: pegaspargase) was developed by chemical modification of native L-asparaginase with polyethylene glycol (PEG) and is expected to play an important role in Japan as a first-line treatment for ALL. Due to the pegylation the half-life of SHP674 becomes longer than that of native L-asparaginase. It has been shown that one dose of SHP674 maintains plasma asparaginase activity levels exceeding the lowest effective plasma asparaginase activity (0.1 IU/mL) for 2 to 3 weeks, depleting asparagine for a long time.[10,11] Therefore, SHP674 is expected to considerably decrease the number of doses in remission induction therapy and consolidation therapy, reducing the burden for patients and health care workers. Additionally the chemical modification with PEG may reduce the immunogenicity of native L-asparaginase.

SHP674 can also be administered to patients who are allergic to native L-asparaginase such as Leunase®. In addition, randomized comparative studies in patients with untreated ALL that were conducted outside Japan showed that SHP674 had a similar safety profile to native L-asparaginase and that there were no differences in efficacy between SHP674 and native L-asparaginase.[10]

1.3.1 Development Status of SHP674 in the United States and Europe

In the United States, SHP674 was approved for marketing in February 1994 as a second-line drug for the treatment of ALL after the onset of hypersensitivity to native L-asparaginase. After that, SHP674 was approved as the first-line drug for the treatment of ALL in 2006.[10,12-15]

SHP674 liquid formulation had been authorized by centralized review procedure in 28 countries in the EU and 3 countries in the European Economic Area (EEA) in first line treatment of ALL on 14 January, 2016. The lyophilized formulation of SHP674 was shown to exert pharmacokinetic/pharmacodynamic actions similar to those of the liquid formulation of SHP674 in October 2017 based on the analysis recommended by the Committee for Medical Products for Human Use (CHMP) of the European Medicines Agency (EMA) and the demonstration of comparability performed through comprehensive analytical and nonclinical comparability assessments. Accordingly, the additional dosage form (lyophilized formulation) was approved for SHP674 by centralized review procedure in 28 countries in the EU and 3 countries in the EEA on December 8, 2017.

1.4 Nonclinical Study Results

Depletion of asparagine by L-asparaginase causes cytotoxicity of lymphoblastic tumor cells, pancreatic cancer cell lines, and ovarian cancer cell lines. Treatment of diseased animals with SHP674 extends survival independent of route of administration.

Pegylation has been proven to reduce drug clearance and degradation and development of anti-drug antibodies. Pegylation extends the half-life of enzyme activity, resulting in a lower dosage schedule with longer administration intervals.

The pharmacokinetics of SHP674 were linear over the dose range tested. The clearance and the distribution volume of SHP674 were small as expected for a protein with a high molecular weight. The volume of distribution was equivalent to blood volumes in all the species, indicating that SHP674 is not distributed outside the systemic circulation. SHP674 did not cross the blood barrier in monkey, and there is a low potential to cross the placental barrier.

There is very limited information about the metabolism and elimination of SHP674. Available study data suggest that SHP674 is cleared by mechanisms other than urinary excretion. Possible mechanisms for its elimination include proteolysis and removal from plasma by the reticuloendothelial system or mononuclear phagocyte system. Metabolism mediated by the liver and excretion through the bile also cannot be excluded.

The main findings in single-dose and/or repeat-dose toxicology studies in mice, rats, and dogs were decreased body weight, slight decrease in spleen weight, sporadic fatty infiltration of hepatocytes without cell necrosis or incidence on the liver functions. No effects on circulating lymphocytes were observed.

Little information is available on the genotoxicity or clastogenicity of SHP674. Available data from Ames tests suggest SHP674 is not genotoxic. L-asparaginase did not induce karyotype abnormalities in pregnant rabbits and in their progeny.

Classical reproductive studies have not been performed with SHP674. Nevertheless, results obtained in vivo or in vitro studies in rats or rabbits gave some evidence of embryotoxic/teratogenic potency of L-asparaginase. No juvenile animal toxicology studies have been performed.

The lyophilization process had no impact on the nonclinical pharmacokinetics, pharmacodynamics, or anti-drug antibody development of the drug and consequently, the safety and effectiveness of the drug product.

Taken together, SHP674 exerted a selective killing effect on leukemia cells by depleting asparagine, leaving healthy cells relatively unharmed, and prolonged survival of diseased animals. The toxicology studies demonstrate that SHP674 is well tolerated and does not have toxic effects (other than

embryotoxicity) at clinically relevant doses. These data support the use of SHP674 for the treatment of ALL.

1.5 Clinical Study Results

1.5.1 Outline of Foreign Clinical Studies

The outline of the 3 major clinical studies of SHP674 conducted outside Japan (Studies AALL07P4, DFCI 11-011, and CCG-1962) is described below.

In Study AALL07P4, 163 subjects with high risk ALL received investigational product (SHP674, 54 subjects; 2100 IU/m^2 EZN-2285 [recently approved in the United States that has an SC linker, which is novel and different from the SS linker used in SHP674, at the binding site of L-asparagine and PEG], 68 subjects; 2500 IU/m^2 EZN-2285, 41 subjects). The primary objective of the study was to assess the pharmacokinetic comparability of SHP674 versus EZN-2285 intravenously administered during remission induction therapy and consolidation therapy to patients with high risk ALL receiving an augmented BFM treatment regimen.

In Study DFCI 11-001, 237 subjects with previously untreated ALL or malignant lymphoma (ALL, 228 subjects; malignant lymphoma, 9 subjects) received investigational product (SHP674, 119 subjects; 2500 IU/m^2 EZN-2285, 118 subjects). The primary objectives of the study were (1) to assess toxicity following the administration of SHP674 or EZN-2285 and (2) to determine and compare serum asparagine activity levels following the administration of SHP674 and EZN-2285.

In Study CCG-1962, of 118 subjects with newly diagnosed, untreated ALL, 59 received SHP674 and 59 received Elspar® (native L-asparaginase preparation). The primary objectives of the study were (1) to compare the safety of SHP674 with that of Elspar® and (2) to determine whether the incidence of high-titer anti-drug antibodies (ADA) (ADA ratio [ratio of ADA titer relative to the negative control titer] ≥2.5) in children treated with SHP674 was decreased by ≥50% compared to Elspar®.

Data on SHP674 and Elspar® obtained from the 3 studies AALL07P4, DFCI 11-011, and CCG-1962 are described in the following sections.

1.5.1.1 Study AALL07P4

Subjects enrolled in the study received IV doses of SHP674 2500 IU/m^2 for at least 1 hour on Day 4 of remission induction therapy (the start day of remission induction therapy was regarded as Day 1) and Day 15 (the start day of consolidation therapy was regarded as Day 1) and Day 43 of consolidation therapy. Plasma asparaginase activity was assessed on Days 4 (pre-dose, 5 minutes post-dose, 4 hours post-dose), 5, 6, 8, 15, 22, and 29 of remission induction therapy and on Days 15 (pre-dose, 5 minutes post-dose, 4 hours post-dose), 16, 17, 22, 29, 36, and 43 of consolidation therapy. As a result, the percentage of subjects with a plasma asparaginase activity of ≥0.1 IU/mL on Days 22 and 29 (18 and 25 days after the administration of SHP674) of remission induction therapy was 95.3% and 29.5%, respectively. The median plasma half-life of SHP674 was 4.4 days. The median plasma asparagine concentration remained below the lower limit of quantification of the assay (0.05 μg/mL) until Day 29 of remission induction therapy.

Samples for immunogenicity assessment were collected on Day 4 (pre-dose) and Day 29 of remission induction therapy; Day 15 (pre-dose) and Day 43 of consolidation therapy; Day 2 (pre-dose) and Day 22 of the first and second interim maintenance therapy (the second therapy was received only by subjects categorized as slow early responders); Day 4 (pre-dose) and Day 43 of the first and second late

consolidation therapy (the second therapy was received only by subjects categorized as slow early responders); and Day 1 of Cycles 1 and 2 of maintenance therapy. After the administration of SHP674, ADA was detected in 5 of 50 subjects (10%) and 6 of 26 subjects (23.1%), respectively, but no neutralizing activity was observed in any of the subjects.

1.5.1.2 Study DFCI 11-001

Subjects enrolled in the study received IV doses of SHP674 2500 IU/m^2 on Day 7 of remission induction therapy and subsequently every 2 weeks from Day 1 of central nervous system preventive therapy (Day 8 of the first consolidation therapy for subjects categorized in the very high-risk group). The serum asparaginase activity reached a maximum level at the first measurement point after the start of administration of SHP674 (5 to 10 minutes post-dose) and decreased thereafter. The percentage of subjects who had a serum asparaginase activity of ≥0.1 IU/mL 18 days after the first dose of SHP674 (Day 7 of remission induction therapy) was 93.5%. Following repeated doses of SHP674 every 2 weeks after remission induction therapy, the trough serum asparaginase activity increased to plateau. Among subjects who had evaluable pharmacokinetic data at 1 or more time points after remission induction therapy, the percentage of subjects with a trough serum asparaginase activity of ≥0.1 IU/mL was 99.0%.

Samples for ADA measurement were collected on Day 7 (pre-dose) and Day 32 of remission induction therapy, Day 8 (pre-dose) of the first consolidation therapy (only for subjects categorized in the very high-risk group), and before the administration of SHP674 in central nervous system preventive therapy and the second consolidation therapy. After the administration of SHP674, anti-asparaginase antibodies and anti-PEG antibodies were detected in 10 of 54 subjects (18.5%) and 11 of 66 subjects (16.7%), respectively, but no neutralizing activity was observed in any of the subjects.

1.5.1.3 Study CCG-1962

Subjects enrolled in the study received a single intramuscular (IM) dose of SHP674 2500 IU/m^2 on Day 3 of remission induction therapy and the first and second delayed intensification therapy; or IM doses of Elspar® (native L-asparaginase) 2500 IU/m^2 (9 doses in remission induction therapy and 6 doses each in the first and second late consolidation therapies). Serum asparaginase activity was assessed before dosing and on Days 7, 14, 21, 28 of remission induction therapy and on Days 0, 7, 14, 21, and 28 of the first and second late consolidation therapy. In the remission induction therapy phase, the serum asparaginase activity following the administration of SHP674 reached a peak on Day 5, with a mean value of 1.0 IU/mL. The elimination half-life from the IM injection site was 5.8 days. The percentage of subjects with a serum asparaginase activity of ≥0.1 IU/mL on Day 21 of the first and second late consolidation therapy was 91% and 93%, respectively. Serum asparagine concentrations rapidly decreased until 4 days after the first dose of SHP674 and remained at low levels until approximately 3 weeks after the first dose. The elimination of Elspar® after the first dose in the remission induction therapy phase was assessed with data from 1 subject who provided multiple samples. The serum asparaginase activity reached a peak (2.0 IU/mL) 4 hours after the IM injection of Elspar®. The elimination half-life was 1.1 days. The percentage of subjects with a serum asparaginase activity of ≥0.1 IU/mL on Day 21 of the first and second late consolidation therapies was 25% and 28%, respectively.

In addition, samples for the assessment of the production of ADA were collected at the same time points as for serum asparaginase activity. As a result of the assessment, the percentage of subjects with high-titer

ADA during the first late consolidation therapy was 15% (7 of 46 subjects) in the Elspar® group and 6% (3 of 49 subjects) in the SHP674 group. The percentage of subjects with high-titer ADA during the second late consolidation therapy was 2% (1 of 44 subjects) in the Elspar® group and 11% (5 of 45 subjects) in the SHP674 group. The asparaginase activity at the time point when the highest titer was reported was assessed to determine the effects of high-titer antibodies in both groups. As a result, although the number of subjects was small, an asparaginase activity of ≥0.1 IU/mL was maintained in more subjects in the SHP674 group than in the Elspar® group in the presence of high-titer ADA.

1.5.2 Efficacy of SHP674 in Foreign Clinical Studies

In Study AALL07P4, the presence or absence of minimal residual disease, complete remission (CR) rate, event-free survival rate, and disease-free survival rate and overall survival rate after CR were assessed at the end of remission induction therapy (Day 29). In the SHP674 group, 74.1% of the subjects (40 of 54 subjects) were negative for minimal residual disease, and the CR rate was 92.6% (50 of 54 subjects). At 4 years, the event-free survival rate was 81.8%, the disease-free survival rate was 85.5%, and the overall survival rate was ≥90%.

In Study DFCI 11-001, the presence or absence of minimal residual disease, CR rate, disease-free survival rate, and overall survival rate were assessed at the end of remission induction therapy (Day 32). In the SHP674 group, 87.9% of the subjects (80 of 91 subjects) had low end-induction MRD (defined as <0.001 by PCR), and the CR rate was 95.7% (110 of 115 subjects). At 1 year, the event-free survival rate was 98.0%, the disease-free survival rate was 98.9%, and the overall survival rate was 100%.

Part of the efficacy assessments conducted in Study CCG-1962 is described in Section 1.5.1.3. Lymphoblasts were depleted more rapidly in the SHP674 group than in the Elspar® group from Day 7 to Day 14 of remission induction therapy. The event-free survival rates at 3, 5, and 7 years were 83%, 78%, and 75% in the SHP674 group and 79%, 73%, and 66% in the Elspar® group.

1.5.3 Safety of SHP674 in Foreign Clinical Studies

In Study AALL07P4, TEAEs were reported in 48 of 52 subjects (92.3%) and drug-related TEAEs were reported in 44 subjects of 52 subjects (84.6%) in the SHP674 group. Grade 3 or 4 TEAEs and drug-related TEAEs were reported in 90.4% (47 of 52 subjects) and 76.9% (40 of 52 subjects) of the subjects, respectively.

The drug-related TEAEs that were reported with high incidence (≥15%) in subjects in the SHP674 group were hyperglycaemia (42.3%), blood bilirubin increased (42.3%), neutrophil count decreased (32.7%), alanine aminotransferase increased (19.2%), anaphylactic reaction (19.2%), white blood cell count decreased (19.2%), activated partial thromboplastin time prolonged (17.3%), and febrile neutropenia (15.4%).

The Grade 3 or 4 drug-related TEAEs that were reported with high incidence (≥15%) in subjects in the SHP674 group were neutrophil count decreased (32.7%), anaphylactic reaction (19.2%), white blood cell count decreased (19.2%), alanine aminotransferase increased (17.3%), hyperglycaemia (15.4%), and febrile neutropenia (15.4%).

The overall safety profile observed in Study AALL07P4 was consistent with the profiles of other asparaginase preparations.

In Study DFCI 11-01, TEAEs and drug-related TEAEs were reported in all of the 119 subjects in the SHP674 group. Grade 3 or 4 TEAEs and drug-related TEAEs were reported in 114 subjects (95.8%) and 104 subjects (87.4%), respectively. The drug-related TEAEs that were reported with high incidence (≥15.0%) in subjects in the SHP674 group were hypoalbuminaemia (80.7%), alanine aminotransferase increased (52.1%), aspartate aminotransferase increased (39.5%), hypertriglyceridaemia (36.1%), blood fibrinogen decreased (25.2%), blood bilirubin increased (23.5%), lipase increased (23.5%), hyperglycaemia (21.8%), amylase increased (16.8%), hypoglycaemia (16.8%), pancreatitis (16.8%), and febrile neutropenia (15.1%).

The Grade 3 or 4 drug-related TEAEs that were reported in ≥5% of the subjects in the SHP674 group with high incidence (≥15%) were alanine aminotransferase increased (35.3%), hypertriglyceridaemia (30.0%), hypoalbuminaemia (26.1%), lipase increased (20.2%), aspartate aminotransferase increased (19.3%), hyperglycaemia (17.6%), blood fibrinogen decreased (17.6%), and febrile neutropenia (15.1%).

The TEAEs reported in Study DFCI 11-01 were consistent with those specific to asparaginase preparations.

In Study CCG-1962, data on Grade 3 or 4 nonhematologic toxicity were collected. The incidence and types of Grade 3 or 4 TEAEs that were reported during the period of treatment with asparaginase (remission induction therapy, first and second late consolidation therapy) were similar in both groups and similar to those observed with other treatment protocols for low-risk and standard-risk ALL.

1.6 Risks and Benefits

1.6.1 Risks

Risks of SHP674 include attenuation or loss of drug efficacy due to anti-SHP674 antibody development and the potential for hypersensitivity, which are typical of all foreign proteins (L-asparaginase enzymes). Other risks include toxicities associated with the impairment of protein synthesis (e.g., pancreatic-, hepatic-, and coagulation-related abnormalities), glucose intolerance, CNS toxicity, myelosuppression, hyperammonemia, and toxicities caused by concomitant drugs (including other anticancer agents).

1.6.2 Benefits

The purpose of asparaginase therapy in ALL is to deplete circulating asparagine amino acid, which ALL cells are unable to synthesize constitutively. This concept has been well established in ALL treatment, and asparaginase is a standard and key component of ALL therapy.

Pegylated asparaginase has advantages over native L-asparaginase. First, the pharmacokinetics of pegylated asparaginase are more favorable than those of native L-asparaginase (longer half-life with correspondingly less frequent drug administrations). Pegylated asparaginase is thus expected to reduce the burden for patients and health care workers, requiring a lower number of doses.

SHP674 is able to deplete plasma asparagine even in the presence of antibodies to native L-asparaginase. In addition, SHP674 is less immunogenic because of pegylation and can be used in patients who have become hypersensitive to native L-asparaginase (the second-line population) to deplete plasma asparagine. Inability to complete planned asparaginase therapy due to hypersensitivity is known to correlate with poor outcome. SHP674 can be continuously administered to patients who are hypersensitive to native L-asparaginase and constitute a major contribution to the care of these patients.

Data from previous studies have shown SHP674 has a similar safety profile to native L-asparaginase. More recent studies DFCI 11-001 and AALL07P4 provided more updated data and information regarding the safety and efficacy profiles for SHP674. SHP674 is able to deplete plasma asparagine in patients who are naïve to asparaginase therapy or who are continuing asparaginase therapy and in whom there is no evidence of allergy or the development of antibodies to SHP674 (the first-line population) and widely used as the first-line drug in clinical practice in Europe and the United States. Thus, SHP674 is intended to be the first-line treatment for ALL in Japan, which could also be used for patients with hypersensitivity to native L-asparaginase.[12]

1.7 Background to the Study Plan

SHP674 has been approved in foreign countries, but the development of the drug has not been started in Japan. As mentioned in Section 1.6.2, there are patients who have a difficulty in continuing the use of the native L-asparaginase Leunase® because of allergic reactions such as anaphylactic shock, which prevents the patients from completing treatment. In addition, the blood half-life of Leunase® is as short as 1.24±0.17 days, and the drug needs to be administered daily or every other day.

SHP674 has immunogenicity reduced by pegylation and can be administered to patients who are allergic to Leunase®. SHP674 is expected to play an important role as an alternative drug for patients who have allergic reactions to Leunase® in Japan. In addition, SHP674 has a blood half-life prolonged by pegylation (5.73±3.24 days), which allows administration every 14 days. 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.

With the above background, the 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 has been designed to obtain the marketing approval of SHP674 in Japan.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Study Objectives

2.1.1 Primary Objective

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.

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.

2.1.2 Secondary Objectives

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.

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]

2.2 Endpoints

2.2.1 Primary Endpoints

Part 1

– Incidence and nature of treatment-emergent adverse events (TEAEs) and SHP674-related TEAEs

that occur or worsen 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.

2.2.2 Rationale for the Primary Endpoint

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.

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.[16] 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.

2.2.3 Secondary Endpoints

Part 1

– Safety
  • Incidence and nature of treatment-emergent adverse events (TEAEs) and drug-related TEAEs
  • Laboratory values
  • Vital signs
– PK
  • PK parameters
– Immunogenicity
  • ADA (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
  • 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

- Vital signs

– PK
  - PK parameters

– Immunogenicity
  - ADA (anti-SHP674 antibody) 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

3 STUDY DESIGN

3.1 Study Design

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). The dosing schedule of each drug including SHP674 is outlined in Table 7-1 to Table 7-3.

3.1.1 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 SR or IR will receive total 3 doses of SHP674 and those categorized as HR will receive total 8 doses of SHP674 during the tolerability assessment period and the treatment period. The outline of the study design in Part 1 is shown in Figure 3.1-1. 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.[17] 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

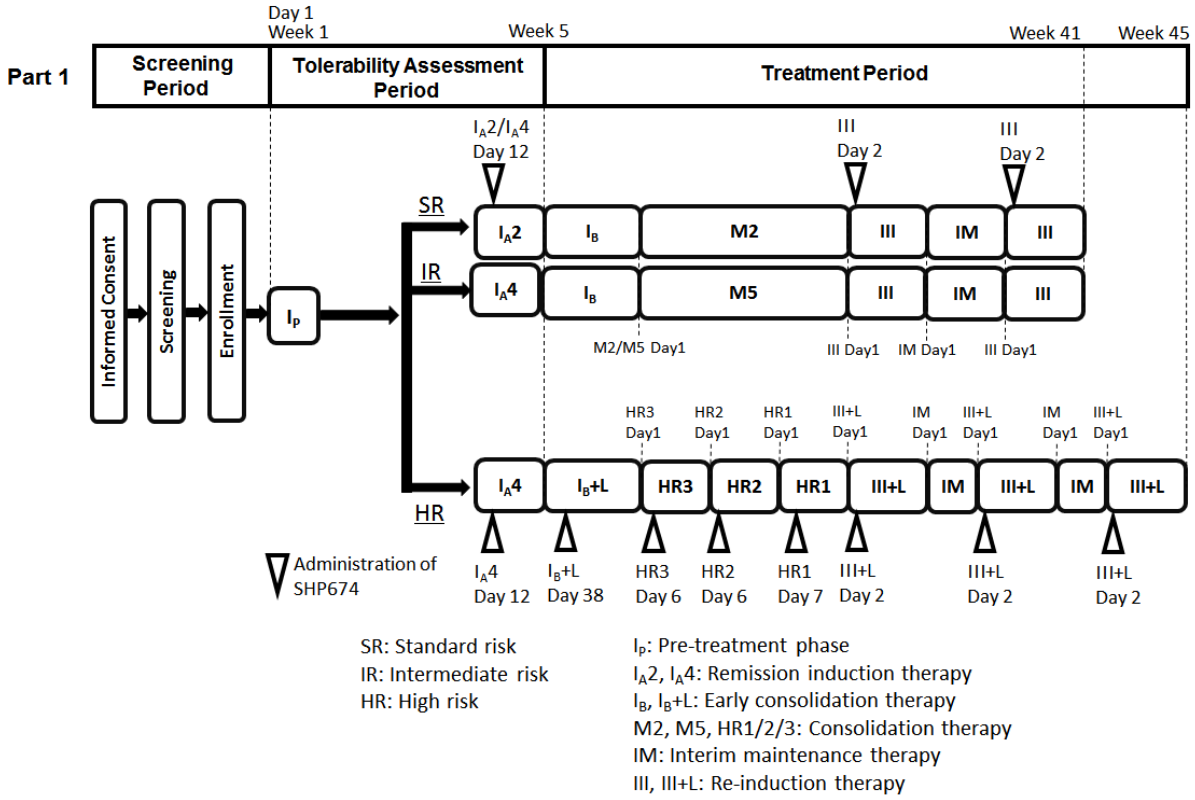
complete the tolerability assessment period will move to the treatment period and continue to receive SHP674. The outline of each treatment phase is shown in Figure 3.1-3.

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 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 procedure are described in Section 7.5.4).

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 3.1-1 Outline of Study Design in Part 1



3.1.2 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 Figure 3.1-2. 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 3.1-3.

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 pharmacokinetics of SHP674 at the dose shown to be tolerated in Part 1.

Figure 3.1-2 Outline of Study Design in Part 2

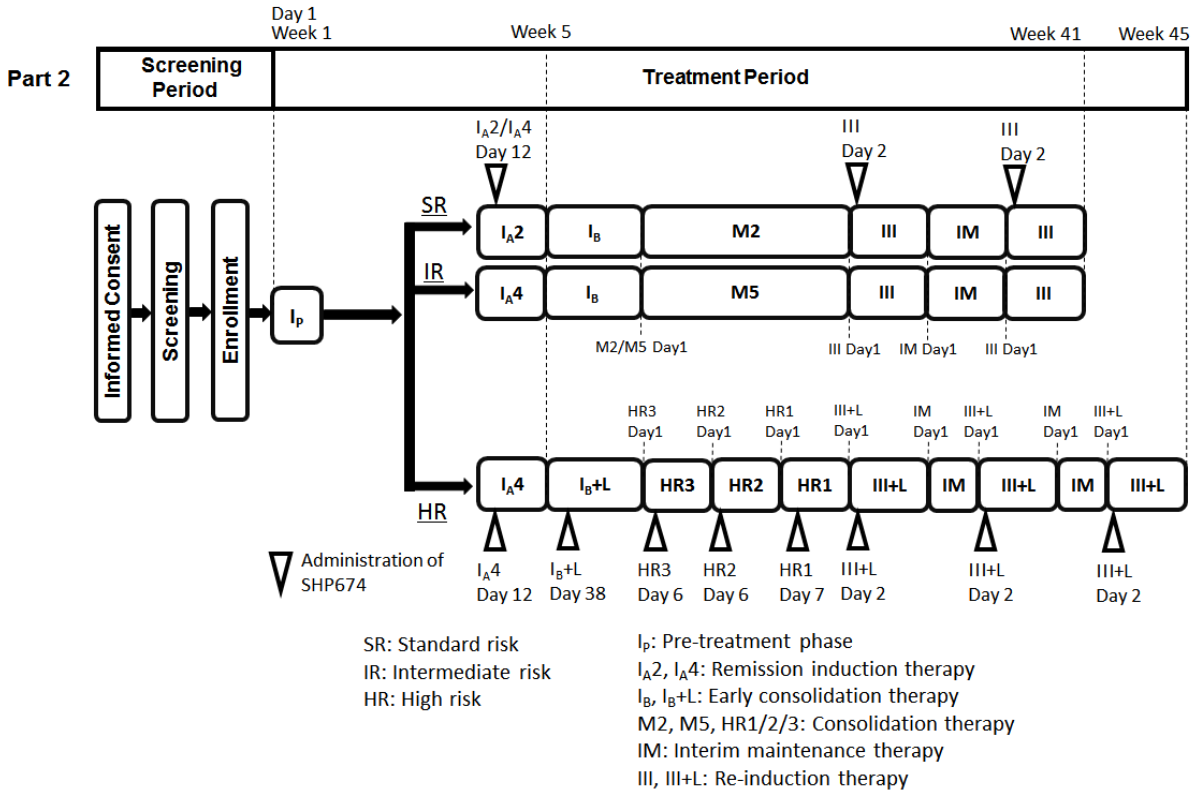
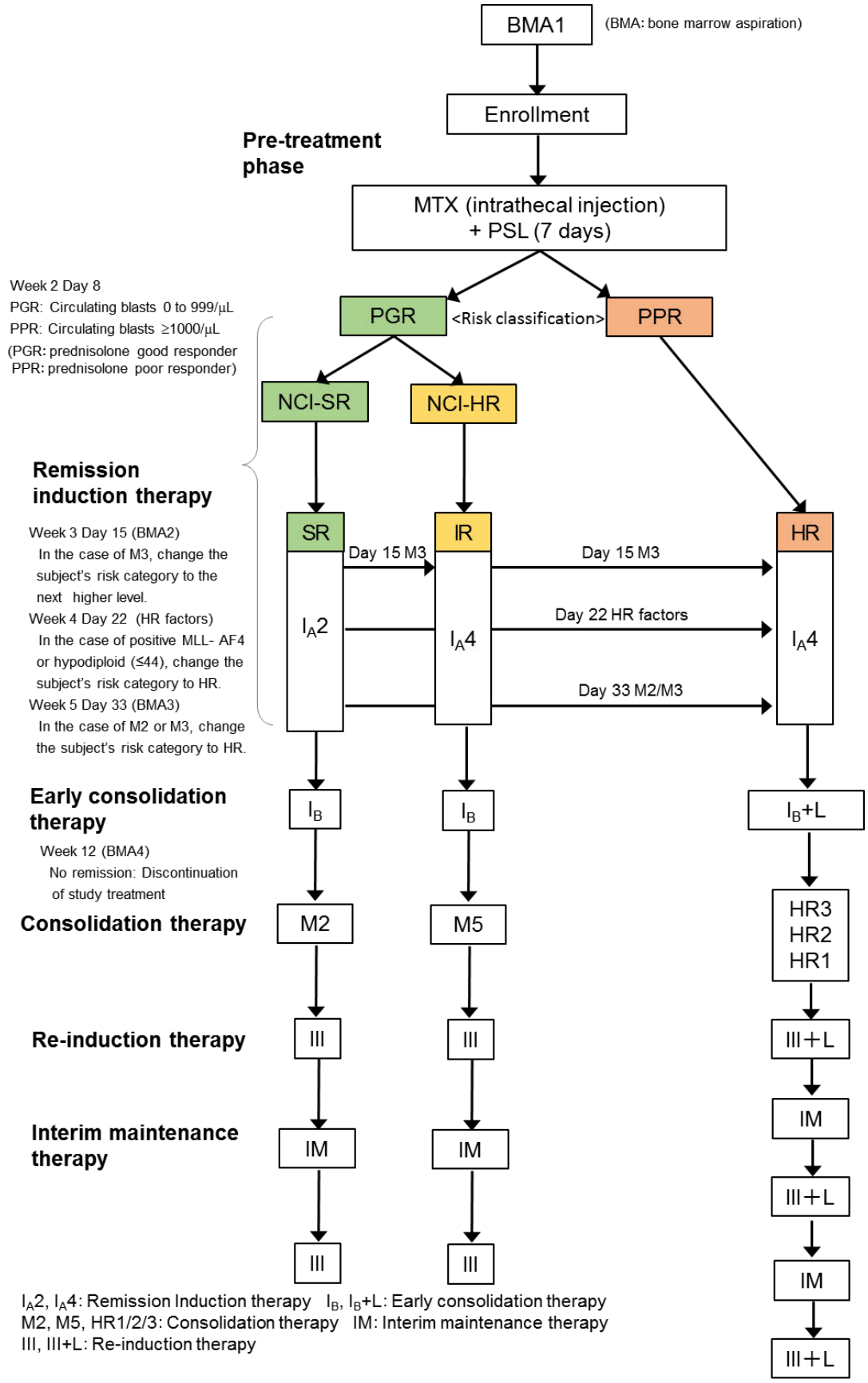


Figure 3.1-3 Outline of Each Treatment Phase



3.1.3 Risk Classification

Subjects who are newly diagnosed with ALL will be stratified into the SR, IR, or HR group according to the risk classification criteria based on the comprehensive assessment from the pre-treatment phase through remission induction therapy. The ALL risk classification used in this study is presented in Table 3.1.3-1. The NCI classification is presented in Table 3.1.3-2.

Table 3.1.3-1 Criteria for Risk Classification

SR	Subject meets all of the following criteria: ・Not categorized as HR according to this classification. ・Prednisolone-good responder (PGR)[a)] ・Categorized as SR per NCI classification (NCI-SR). ・ M1 or M2 marrow [b)] at bone marrow examination on Day 15 of remission induction therapy (BMA2).
IR	Subject meets any of the following criteria: ・Categorized as other than HR according to this classification, PGR, and HR per NCI classification (NCI-HR). ・Categorized as PGR and NCI-SR; and M3 marrow[b)] at bone marrow examination on Day 15 of remission induction therapy (BMA2).
HR	Subject meets one or more of the following criteria: ・CNS-3[c)] on Day 1 of the pre-treatment phase. ・Categorized as a prednisolone-poor responder (PPR)[a)] on Day 8 of remission induction therapy. ・Categorized as PGR and NCI-HR; and M3 marrow[b)] on Day 15 of remission induction therapy (BMA2). ・Assessed as having refractory disease at BMA3. ・ *KMT2A-AFF1* (*MLL-AF4*) fusion gene-positive (to be determined before the start of treatment on Day 22 of remission induction therapy). ・Hypodiploid (≤44 chromosomes) (to be determined before the start of treatment on Day 22 of remission induction therapy)

SR, standard risk; IR, intermediate risk; HR, high risk
a: See Section 8.3.4.
b: Bone marrow status is categorized as follows according to the percentage of blasts in bone marrow:
· M1 marrow: <5%
· M2 marrow: 5% to ≤25%
· M3 marrow: >25%
c: See Section 3.1.4.1.1. In this study, subjects with CNS-3 status meet the withdrawal criterion.

Table 3.1.3-2 Criteria for NCI Classification

		Circulating White Blood Cell Count[a)]	
		<50000/μL	≥50000/μL
Age	1 to ≤9 years	SR	HR
	<1 year, ≥10 years	HR	HR

a Categorized based on the maximum value obtained at the investigative site before the start of treatment.

3.1.3.1 Change of Risk Category

A subject's risk category needs to be changed in the following cases:

- If a subject is considered a prednisolone poor responder (PPR) on Day 8 of remission induction therapy, the subject's risk category will be changed to HR.
- If a subject is assessed as having M3 marrow at bone marrow examination on Day 15 of remission induction therapy (BMA2), the subject's risk category will be changed to the next higher level (from SR to IR, from IR to HR).

- If a subject is shown to be *KMT2A-AFF1* (*MLL-AF4*) fusion gene-positive or hypodiploid (≤44 chromosomes) before the start of treatment on Day 22 of remission induction therapy, the subject's risk category will be changed to HR.
- If a subject is assessed as having refractory disease at BMA3, the subject's risk category will be changed to HR.

3.1.4 Criteria for Evaluation of Organ Involvement

3.1.4.1 Central Nervous System (CNS) Involvement

3.1.4.1.1 Classification of CNS Status (NCCN Guidelines[18])

- CNS-1: No lymphoblasts in cerebrospinal fluid (CSF) regardless of white blood cell count.
- CNS-2: WBC <5/μL in CSF with presence of lymphoblasts.
- CNS-3: WBC ≥5/μL in CSF with presence of lymphoblasts.

If the patient has leukemic cells in the peripheral blood and the lumbar puncture is traumatic and WBC ≥5/μL in CSF with blasts, then compare the CSF WBC/RBC ratio to the blood WBC/RBC ratio. If the CSF ratio is at least 2-fold greater than the blood ratio, then the classification is CNS-3; if not, then it is CNS-2.

3.1.4.1.2 Test for Determination of CNS Status

When determining the presence or absence of CNS involvement at the initial visit, the first cerebrospinal fluid examination must be performed simultaneously with the first intrathecal injection to prevent the invasion of the marrow cavity by blasts associated with lumbar puncture. The presence or absence of blasts must be determined only with Cytospin samples. Not only white blood cell count but also red blood cell count should be calculated when determining the number of cells in the cerebrospinal fluid. Search for findings such as tumor lesions by brain tomography (MRI or CT) is also essential before the start of treatment.

3.1.5 Rationale for Study Design

The position of L-asparaginase preparations in the treatment of ALL has been established based on treatment results obtained in and outside Japan. Data on SHP674 has been obtained from multiple clinical studies outside of Japan and were found to be comparable to native L-asparaginase, this study will be conducted as a multicenter, non-randomized, open-label, single arm Phase 2 clinical study.

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. The tolerability assessment period is defined as the period until the end of remission induction therapy to assess tolerability at least for a period corresponding to approximately 5 half-lives of SHP674 (approximately 25 days). Due to potential increased risk of hypersensitivity when switching from SHP674 to native L-asparaginase patients treated in Part 1 of the study will continue to receive SHP674 for all subsequent treatment phases where asparaginase administration is required.

The study will be further continued as Part 2 after the tolerability of SHP674 is established in Part 1.

3.2 Enrollment of Subjects

The investigator or subinvestigator will enroll subjects according to the procedure described below.

1) If the potential subject is an adult, the investigator or subinvestigator will fully explain the nature of the study to the potential subject and obtain his or her written informed consent for participation in the study. If the potential subject is a child, the investigator or subinvestigator will fully explain the nature of the study to the potential subject and his or her legally acceptable representative and obtain written informed consent for participation in the study from the legally acceptable representative. In addition, the investigator or subinvestigator will obtain adequate oral or written assent from the potential subject as far as possible.
2) The investigator or subinvestigator will assess the subject for all the inclusion and exclusion criteria to determine eligibility. If the subject is considered eligible, the investigator or subinvestigator will enter relevant information on the subject into an interactive web response system (IWRS) according to the written procedure developed elsewhere. Study treatment will be started within 7 days after enrollment. Subjects enrolled once cannot be re-enrolled. If the subject is ineligible for enrollment, the investigator or subinvestigator will enter SID, date of obtaining informed assent or consent, sex, and the reason for ineligibility into the eCRF.

3.3 Target Sample Size

Part 1 = 3 to 6 evaluable subjects

Part 2 = 22 subjects

3.4 Planned Study Period

May 2019 to December, 2022

-A snapshot of data will be taken for analysis of all available endpoints after all subjects completed remission induction therapy. The clinical study report (CSR) will be based on the data from the period of remission induction phase. Additional safety, PK and survival final analysis of all secondary [redacted] endpoints will be performed after all subjects complete the study (365 [±7] days after the first dose of SHP674 or at the time all subjects complete the study) and submitted as an addendum to the CSR.

4 SUBJECT ELIGIBILITY CRITERIA

4.1 Target Disease

ALL

4.1.1 Diagnosis of ALL

ALL is defined as a condition in which lymphoblasts account for at least 25% of all nucleated cells in bone marrow.

B-ALL is defined as ALL that meets the immunological criteria for diagnosis based on immunological marker findings (see Attachment 5 to the protocol [supplement]), according to the WHO Classification 2017.

4.2 Inclusion Criteria

Subjects enrolled in the study must meet all of the following criteria:

1) For Part 1, personally provided informed assent or written informed consent. If informed assent is obtained from a subject, written informed consent should be 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 should be obtained from the subject as far as possible even if written informed consent is 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 (see Attachment 5 to the protocol [supplement]);
5) No prior therapy for malignant tumor such as chemotherapy and radiation therapy before signing the informed consent;
6) The following laboratory criteria are met at the time of screening:
    - AST and ALT ≤10 × age-specific upper limit of normal (ULN)
    - D-Bil <1.5 mg/dL
    - Serum creatinine ≤1.5 × age-specific ULN
    - Corrected serum calcium ≤11.5 mg/dL
    - Left ventricular ejection fraction ≥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 must 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 must have a negative serum or urinary pregnancy test result at screening test.

    Note:
    - *A woman of childbearing potential is defined as a woman who has experienced her first menstruation, has not undergone hysterectomy, bilateral tubal ligation, or bilateral ovariectomy*

and is not postmenopausal. Postmenopausal status is defined as amenorrhea of ≥12 consecutive months with no specific causes

- *Since there is a potential for an indirect interaction between SHP674 and oral contraceptives, the concomitant use of SHP674 and oral contraceptives is not recommended. Another, non-oral contraceptive method should be used in women of childbearing potential.*

4.3 Exclusion Criteria

Subjects must be excluded from participating in this study if they meet any of the following criteria:

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 will be allowed);
8) Positive for HBs antigen, HCV antibody, or HIV antibody. Subjects who are negative for HBs antigen but positive for HBc antibody and/or HBs antibody will undergo an HBV DNA test and will be excluded from the study if they are 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 polyethylene glycol (PEG) or PEG-based drugs;
11) Current symptoms or signs of CNS involvement (e.g., cranial nerve symptoms such as facial palsy), with CNS disease detected on CT or MRI;
12) Pregnant (or planning to become pregnant in near future) or breastfeeding women (breastfeeding women will be excluded from the study even if they stop their breastfeeding);
13) History of previous malignancy, other concurrent malignancy, or secondary ALL; or
14) Other inadequacy determined by the investigator or subinvestigator.

5 STOPPING RULES AND PROCEDURES

5.1 Subject Withdrawal

The investigator or subinvestigator will take appropriate actions for subjects who are withdrawn from the study or treatment in the case of safety issues such as occurrence of an AE. The investigator or subinvestigator will also ensure the safety of withdrawn subjects and conduct an early termination (ET) assessment 30 (+7) days after the last dose of investigational product. If the subject's next therapy starts 30 (+7) days after the last dose of investigational product or earlier, the ET assessment may be conducted within 7 days of the start date of the next therapy. Adverse event information should be collected until 30 (+7) days after the last dose of investigational product.

Subjects who do not return to the investigative site without completing the scheduled assessments after the start of study treatment will be followed up as long as possible, with due consideration of the subject's human rights, to assess safety. The investigator or subinvestigator will make best efforts to keep subjects participating in the study unless there is a medical contraindication or significant deviation from the protocol. However, if the investigator or subinvestigator determines that discontinuation of study treatment is the best interest of the subject, or if the subject decides to withdraw his or her consent, the investigator or subinvestigator will make best efforts to complete sufficient observation and report the results as far as possible.

The investigator or subinvestigator will identify the date of early termination and the reason for early termination and enter the information into the electronic case report form (eCRF).

5.1.1 Withdrawal from the Study

Subjects will be withdrawn from the study if any of the following situations occurs. Withdrawn subjects will not undergo survival follow-up specified in Section 8.24 after withdrawal from the study.

1) The subject is found not to meet the eligibility criteria after the start of the study prior to administration of SHP674 unless the investigator indicate that the participation of the subjects is beneficial and the Sponsor approved the continuation of the subject participation.
2) The subject (or his or her legally acceptable representative) wishes to withdraw consent from the study.
3) The subject cannot undergo necessary observations and examinations for a personal reason before the administration of SHP674 in remission induction therapy.
4) The investigator or subinvestigator determines that the subject should discontinue study treatment because of an AE before the administration of SHP674 in remission induction therapy.
5) A new malignancy is detected in the subject before the administration of SHP674 in remission induction therapy.
6) The subject is found to have MYC translocation-positive ALL before the administration of SHP674 in remission induction therapy.
7) The subject is found to have Philadelphia chromosome-positive (Ph+) or *BCR-ABL1*-positive ALL before the administration of SHP674 in remission induction therapy.
8) The subject cannot receive SHP674 in remission induction therapy.

9) Central nervous system (CNS) involvement status classified as CNS-3 according to the NCCN guidelines at the time of first MTX IT during the pre-treatment phase (see Attachment 6 to the protocol [supplement]).
10) The total dosage of PSL received by the subject in the pre-treatment phase (I_P) is <210 mg/m^2; or the subject has a circulating white blood cell count of ≥100000/μL and a circulating blast count that is ≥1.5-fold that on Day 1 during the period from Day 4 to Day 7, requiring the earlier start of remission induction therapy (including VCR administration on Day 8).
11) The subject requires a treatment for the primary disease that is not specified in the protocol including hematopoietic stem cell transplantation before the administration of SHP674 in remission induction therapy (subjects for whom hematopoietic stem cell transplantation is indicated must be withdrawn from the study before pre-treatment for transplantation).
12) The investigator or subinvestigator determines that the subject should be withdrawn from the study for a reason other than above before the administration of SHP674 in remission induction therapy.
13) The Sponsor determines that the study (the entire study or the study at the investigative site) should be terminated.

5.1.2 Treatment Discontinuation

The protocol-specified treatment will be discontinued if a subject meets any of the criteria below. Subjects treated with SHP674 will be followed for survival as specified in Section 8.24 after treatment discontinuation.

1) The subject is found not to meet the eligibility criteria after the administration of SHP674 in remission induction therapy unless the investigator indicate that the participation of the subjects is beneficial and the Sponsor approved the continuation of the subject participation.
2) The investigator or subinvestigator determines that the subject should discontinue study treatment because of an AE after the administration of SHP674 in remission induction therapy.
3) The subject has relapse of the primary disease (see Section 5.2).
4) A new malignancy is detected in the subject after the administration of SHP674 in remission induction therapy.
5) The subject has no remission at bone marrow examination during early consolidation therapy (BMA4).
6) After receiving the prescribed treatment with SHP674 in remission induction therapy, the subject becomes unable to undergo necessary observations and examinations for a personal reason.
7) The subject is found to have MYC translocation-positive ALL after the administration of SHP674 in remission induction therapy.
8) The subject is found to have Philadelphia chromosome-positive (Ph+) or *BCR-ABL1*-positive ALL after the administration of SHP674 in remission induction therapy.
9) The subject cannot receive SHP674 in any of the treatment phases after remission induction therapy.
10) The administration of VCR, DNR, SHP674, or TIT (for subjects with CNS-2 status) is postponed for ≥15 consecutive days during remission induction therapy (I_A2/I_A4).
11) Early consolidation therapy (I_B/I_B+L) is interrupted for ≥28 days.
12) Re-induction therapy (III/III+L) is interrupted for ≥28 days.
13) The subject cannot start or complete treatment within the periods specified below:

- Early consolidation therapy (I_B/I_B+L) cannot be completed within 18 weeks after the start of remission induction therapy (I_A2/I_A4).
- Consolidation therapy (M2/M5/HR3, HR2, HR1) cannot be completed within 14 weeks after the start of each consolidation therapy.
- Re-induction therapy (III/III+L) cannot be completed within 16 weeks after the start of each re-induction therapy.
- The next treatment phase cannot be started within 6 weeks from the day after the completion of drug treatment in early consolidation therapy (I_B/I_B+L).
- Re-induction therapy (III/III+L) cannot be started within 6 weeks from the day after the completion of drug treatment in consolidation therapy (M2/M5/HR3, HR2, HR1).
- There is an interval of ≥8 weeks between treatment phases in cases other than those listed above.

14) The subject requires a treatment for the primary disease that is not specified in the protocol including hematopoietic stem cell transplantation after the administration of SHP674 in remission induction therapy (subjects for whom hematopoietic stem cell transplantation is indicated must be withdrawn from the study before pre-treatment for transplantation).
15) The subject experiences Grade 3 pancreatitis, hypersensitivity reaction, or thrombosis after the administration of SHP674.
16) The subject experiences the intolerable toxicity that is specified in Section 7.5.2 in Part 1 and does not or is not expected to recover by Day 37 of remission induction therapy.
17) The investigator or subinvestigator determines that the subject should be withdrawn from the study for a reason other than above after the administration of SHP674 in remission induction therapy.

5.2 Definition of Relapsed Disease

[redacted]

5.2.1 Extramedullary Relapse

1) CNS relapse: Development of CNS-3 status or clinical signs of CNS leukemia such as facial nerve palsy, brain/eye involvement, or hypothalamic syndrome [redacted]
2) Other organs: Recurrence of mediastinal enlargement [redacted] At least one of the previously observed lesions is positive on post-treatment PET for subjects who had a positive result on previous PET.

5.3 Premature Termination or Suspension of the Study at the Investigative Site

If the investigator prematurely terminates or suspends the study at his or her site for concerns over the safety of investigational product or for any other reason, the investigator will promptly notify the director of the investigative site in writing, with a detailed written explanation. The director of the investigative site will promptly notify the Sponsor or in-country caretaker and the IRB in writing of the premature termination or suspension and the reason for the decision.

Any of the following circumstances will also result in the premature termination of the study at the investigative site. In such an event, appropriate steps will be taken in a similar manner to the above.

1) The director of the investigative site requests that the protocol be revised based on the IRB's recommendation, but the Sponsor cannot accept it.
2) The IRB consulted by the director of the investigative site concludes that the study should not be continued, and the director of the investigative site orders that the study be terminated.
3) The investigative site has major or continuous violations of GCP, the protocol, or the clinical study agreement.

5.4 Premature Termination or Suspension of the Entire Study

If the entire study is prematurely terminated or suspended, the Sponsor will promptly inform all investigative site directors and the regulatory authority with a detailed explanation of the reason. Upon receipt of the notification, the director of the investigative site will promptly inform the investigator and the IRB of the termination or suspension in writing, with a description of the reason. If the study is prematurely terminated or suspended, the investigator will promptly notify subjects of the termination or suspension and take necessary measures such as providing appropriate medical care.

6 Investigational Product

6.1 Test Drug and Backbone Therapy Drugs Provided by the Sponsor for Investigational Use

6.1.1 Test Drug

Company code: SHP674

Nonproprietary name: Pegaspargase

Molecular weight: 280000 to 300000

Strength and formulation:

A vial containing 3570 IU active ingredient. SHP674 is a white to off-white lyophilized powder and supplied as a sterile, single-use vial.

Drug reconciliation method:

The drug is dissolved in 5.2 mL sterile water for injection to make 750 IU/mL of solution. The composition of lyophilized SHP674 after dissolution is shown in Table 6.1.1-1.

Table 6.1.1-1 Composition of Lyophilized SHP674

Ingredient	Amount per mL (after dissolution)	Function
SHP674 drug substance	750 IU	Active ingredient
Disodium hydrogen phosphate	0.56 mg	Buffer agent
Sodium dihydrogenphosphate	2.58 mg	Buffer agent
Sodium chloride	3.94 mg	Isotonic fluid
Sucrose	42 mg	Stabilizer
Sodium hydroxide	Trace amount	pH adjustment
Hydrochloric acid	Trace amount	pH adjustment

6.1.2 Backbone Therapy Drugs Provided by the Sponsor for Investigational Use

1) Predonine® Tablets 5 mg

Company code: PSL-SER-PO-T

Non-proprietary name: Prednisolone

Chemical name: 11β, 17, 21-Trihydroxypregna-1, 4-diene-3, 20-dione (IUPAC)

Molecular formula: $C_{21}H_2O_5$

Molecular weight: 360.44

Strength and formulation:

Light orange tablets each containing 5 mg prednisolone.

2) Prednisolone Powder 1%

Company code: PSL-SER-PO-P

Non-proprietary name: Prednisolone

Chemical name: 11β, 17, 21-Trihydroxypregna-1, 4-diene-3, 20-dione (IUPAC)

Molecular formula: $C_{21}H_2O_5$

Molecular weight: 360.44

Strength and formulation:

Vials of 100 g power containing 10 mg prednisolone per gram.

3) Predonine® 50 mg (Water-soluble)

Company code: PSL-SER

Non-proprietary name: Prednisolone sodium succinate

Chemical name: Monosodium 11β, 17, 21-trihydroxypregna-1, 4-diene-3, 20-dione 21-succinate (IUPAC)

Molecular formula: $C_{25}H_{31}O_8$

Molecular weight: 482.50

Strength and formulation:

An ampule containing 50 mg prednisolone. The drug is supplied as a lyophilized, sterile, single-use ampule.

Drug reconciliation method:

The ampule contents are dissolved in 1 to 5 mL water for injection or isotonic sodium chloride solution to prepare solution.

Procedure for triple intrathecal therapy (TIT):

Dissolve MTX in distilled water for injection to a concentration of 2.5 mg/mL. Dissolve PSL in distilled water for injection to a concentration of 10 mg/mL. Take the necessary amount of Ara-C in a syringe. Administer MTX, Ara-C, and PSL in one syringe.

4) Endoxan® 500 mg (for Injection)

Company code: CPA-SER

Non-proprietary name: Cyclophosphamide hydrate

Chemical name: N,N-Bis(2-chloroethyl)-3,4,5,6-tetrahydro-2H-1,3,2-oxazaphosphorin-2-amine 2-oxide monohydrate (IUPAC)

Molecular formula: $C_7H_{15}Cl_2N_2O_2P \cdot H_2O$

Molecular weight: 279.10

Strength and formulation:

A vial containing 500 mg cyclophosphamide. The drug is supplied as a sterile, single-use vial.

Drug reconciliation method:

Five milliliters of isotonic sodium chloride solution or water for injection are added per 100 mg of cyclophosphamide (as anhydride) to dissolve. Water for injection should not be used for one-shot administration such as intravenous injection because the solution becomes hypotonic.

5) Leukerin® Powder 10%

Company code: 6-MP-SER

Non-proprietary name: Mercaptopurine hydrate

Chemical name: 1,7-Dihydro-6H-purine-6-thione monohydrate (IUPAC)

Molecular formula: $C_5H_4N_4S \cdot H_2O$

Molecular weight: 170.19

Strength and formulation:

Bottle of 25 g of power containing 100 mg mercaptopurine hydrate per gram.

6) Lastet® Inj. 100 mg/5 mL

Company code: VP-16-SER

Non-proprietary name: Etoposide

Chemical name: (5R,5aR,8aR,9S)-9-{[4,6-O-(1R)-Ethylideneβ-D-glucopyranosyl]oxy}-5-(4-hydroxy-3,5-dimethoxyphenyl)-5,8,8a,9-tetrahydrofuro[3',4':6,7]naphtho[2,3-d][1,3]dioxol-6(5aH)-one

Molecular formula: $C_{29}H_3O_{13}$

Molecular weight: 588.5

Strength and formulation:

A vial (5 mL) containing 100 mg etoposide. The drug is supplied as a sterile, single-use vial.

7) Ifomide® 1 g (for Injection)

Company code: IFO-SER

Non-proprietary name: Ifosfamide

Chemical name: (±)-3-(2-Chloroethyl)-2-[(2-chloroetyl)amino] tetrahydro-2H-1,3 2-oxazaphosphorine 2-oxide (IUPAC)

Molecular formula: $C_7H_{15}Cl_2N_2O_2P$

Molecular weight: 261.09

Strength and formulation:

A vial containing 1 g ifosfamide. The drug is supplied as a sterile, single-use vial.

Drug reconciliation method:

One gram (1 bottle) of ifosfamide is dissolved in 25 mL isotonic sodium chloride solution or water for injection.

8) Decadron® Tablets 0.5 mg/4 mg

Company code: DEX-SER-PO

Non-proprietary name: Dexamethasone

Chemical name: 9-Fluoro-11β,17,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione (IUPAC)

Molecular formula: $C_{22}H_{29}FO_5$

Molecular weight: 392.46

Strength and formulation:

White or light red tablets each containing 0.5 mg or 4 mg dexamethasone.

9) Decadron® Phosphate Injection 6.6 mg

Company code: DEX-SER-IV

Non-proprietary name: Dexamethasone sodium phosphate

Chemical name: 9-Fluoro-11β,17,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione 21-(disodium phosphate) (IUPAC)

Molecular formula: $C_{22}H_{28}FNa_2O_8P$

Molecular weight: 516.40

Strength and formulation:

A vial (2 mL) containing 6.6 mg dexamethasone. The drug is supplied as a sterile, single-use vial.

10) Methotrexate® Tablets 2.5 mg

Company code: MTX-SER

Non-proprietary name: Methotrexate

Chemical name: N-{4-[(2,4-Diaminopteridin-6-ylmethyl)(methyl)amino]benzoyl}-L-glutamic acid (IUPAC)

Molecular formula: $C_{20}H_{22}N_8O_5$

Molecular weight: 454.44

Strength and formulation:

Light yellow-brown tablets each containing 2.5 mg methotrexate.

11) Methotrexate® Injection 1000 mg

Company code: HD-MTX-SER

Non-proprietary name: Methotrexate

Chemical name: N-{4-[(2,4-Diaminopteridin-6-ylmethyl)(methyl)amino]benzoyl}-L-glutamic acid (IUPAC)

Molecular formula: $C_{20}H_{22}N_8O_5$

Molecular weight: 454.44

Strength and formulation:

A vial (10 mL or 40 mL) containing 1000 mg methotrexate. The drug is supplied as a sterile, single-use vial.

6.2 Packaging and Labeling

6.2.1 Package Presentation

SHP674: 1 vial/box

Predonine® Tablets 5 mg: 100 tablets/box

Prednisolone Powder 1%: 1 vial/box

Predonine® 50 mg (water-soluble): 5 ampules/box

Endoxan® 500 mg (for injection): 1 vial/box

Leukerin® Powder 10%: 1 vial/box

Lastet® Inj.100 mg/5 mL: 1 vial/box

Ifomide® 1 g (for injection): 10 vials/box

Decadron® Tablets 0.5 mg/4 mg: 100 tablets/box

Decadron® Phosphate Injection 6.6 mg: 10 vials/box

Methotrexate® Tablets 2.5 mg: 100 tablets/box

Methotrexate® Injection 1000 mg: 1 vial/box

6.2.2 Labeling

All labels for the test drug and the backbone therapy drugs provided by the Sponsor for investigational use will contain the following information:

Label for outer box: Statement that the drug is for investigational use, name and country name of the Sponsor, name and address of the in-country caretaker, company code, lot number, investigational product number, and storage directions

Label for syringe, ampule or vial: a statement to the effect that the drug is for investigational use, name of the Sponsor and the in-country caretaker, company code, lot number, and investigational product number

6.3 Storage Conditions

SHP674: At 2°C to 8°C.

Predonine® Tablets 5 mg: At room temperature.

Prednisolone Powder 1%: At room temperature.

Predonine® 50 mg (water-soluble): At room temperature, protected from light.

Endoxan® 500 mg (for injection): At 2°C to 8°C.

Leukerin® Powder 10%: At room temperature.

Lastet® Inj.100 mg/5 mL: At room temperature.

Ifomide® 1 g (for injection): At room temperature.

Decadron® Tablets 0.5 mg/4 mg: At room temperature.

Decadron® Phosphate Injection 6.6 mg: Store in a cold place, protected from light. Avoid freezing.

Methotrexate® Tablets 2.5 mg: At room temperature, protected from light.

Methotrexate® Injection 1000 mg: The 10-mL preparation should be stored at 15°C to 25°C, protected from light. The 40-mL preparation should be stored at room temperature, protected from light.

6.4 Dispensing, Storage, Management, and Return of Investigational Product

The Sponsor or the in-country caretaker will dispense investigational product to each investigative site through a contractor for transportation selected by the Sponsor or the in-country caretaker after concluding a clinical study agreement with the investigative site. The details of investigational product dispensing will be described in the study pharmacy manual provided to each site prior to the site initiation. Each site will be trained regarding these procedures during the site initiation visit and later on as required. The Sponsor will develop a written procedure for the management of investigational product and submit it to the investigative site.

The investigational product manager at each investigative site will properly store and manage investigational product according to the written procedure and will document the use of investigational product, including inventory, return, and destruction. The investigational product manager will properly check the number of unused and used supplies of the investigational product (including empty vials and boxes) against the investigational product management record. The investigational product manager will return investigational product to the Sponsor or the in-country caretaker after the end of the study or at the time of re-dispensing of investigational product accompanied by batch switch.

The investigational product manager will submit a copy of the investigational product management record to the Sponsor or the in-country caretaker after finalizing the records of use of investigational product.

7 TREATMENT PLAN AND CONCOMITANT TREATMENTS

The outline of the treatment schedule is shown in Table 7-1 to Table 7-3.

Table 7-1 Treatment Schedule for SR

	I_P								I_A2**													
Week		1							2							3						
Day	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
PSL#		▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒
MTX IT		◎*																				
VCR									○							○						
DNR									●							●						
SHP674#													◇									
TIT***, ## Note: (◎) is for subjects with CNS-2 only													◎						(◎)			
CPA#																						
Ara-C																						
6-MP#																						

															I_B						
Week	4							5							6						
Day	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42
PSL#	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒					
MTX IT																					
VCR	○							○													
DNR																					
SHP674#																					
TIT***, ## Note: (◎) is for subjects with CNS-2 only						(◎)						◎									
CPA#															□						
Ara-C																	■	■	■	■	
6-MP#															▒	▒	▒	▒	▒	▒	▒

* If a subject cannot receive intrathecal MTX on Day 1 for a reason such as that the subject's initial visit falls on a weekend, the administration of MTX can be postponed until up to Day 4.
** I_A2 will be from Day 8 (Week 2) to the end of PSL administration on Day 37 (Week 6).
***TIT is allowed to be performed within 3 days of the prescribed day if there is a social reason such as that the prescribed day falls on a weekend or holiday.
To be provided by the Sponsor as an investigational product.
Only PSL will be provided by the Sponsor as an investigational product.
Each symbol represents the day of each drug administration.

Table 7-1 Treatment Schedule for SR (Continued)

	I_B																																		
Week	7							8							9							10							11						
Day	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77
PSL#																																			
MTX IT																																			
VCR																																			
DNR																																			
SHP674#																																			
TIT***, ## Note: (◎) is for subjects with CNS-2 only			◎														◎																		
CPA#																						□													
Ara-C			■	■	■	■				■	■	■	■				■	■	■	■															
6-MP#	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒														

Table 7-1 Treatment Schedule for SR (Continued)

	M2																											
Week	12							13							14							15						
Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
6-MP#	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒
HD-MTX#								◆24h														◆24h						
LV										↓↓↓														↓↓↓				
DEX# (<10 years)																												
DEX# (≥10 years)																												
VCR																												
THP																												
SHP674#																												
CPA#																												
Ara-C																												
MTX#																												
TIT##								◎														◎						

	M2																											
Week	16							17							18							19						
Day	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56
6-MP#	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒
HD-MTX#								◆24h														◆24h						
LV										↓↓↓														↓↓↓				
DEX# (<10 years)																												
DEX# (≥10 years)																												
VCR																												
THP																												
SHP674#																												
CPA#																												
Ara-C																												
MTX#																												
TIT##								◎														◎						

Table 7-1 Treatment Schedule for SR (Continued)

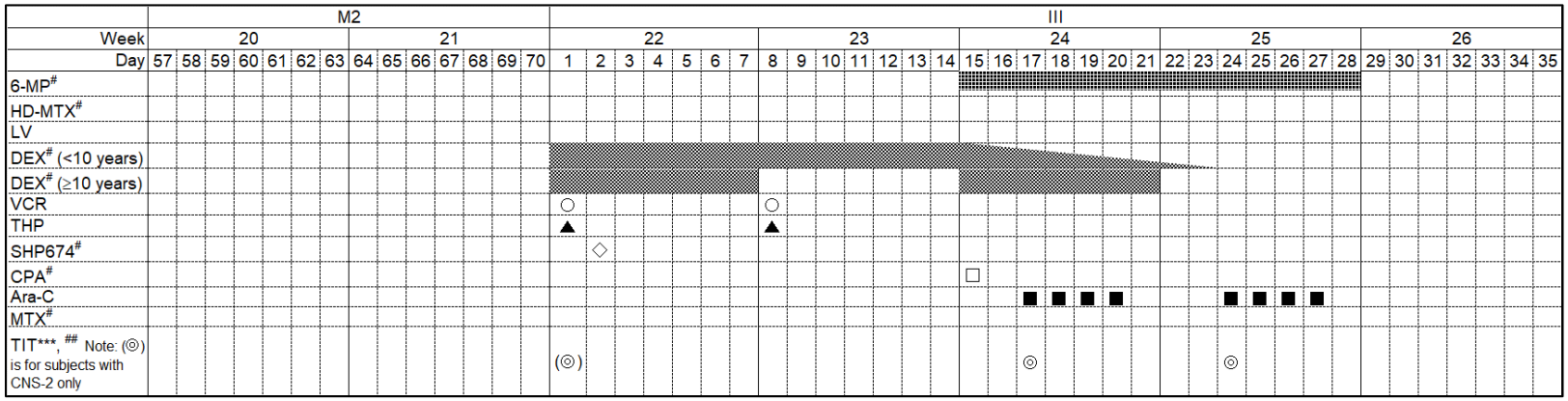


Table 7-1 Treatment Schedule for SR (Continued)

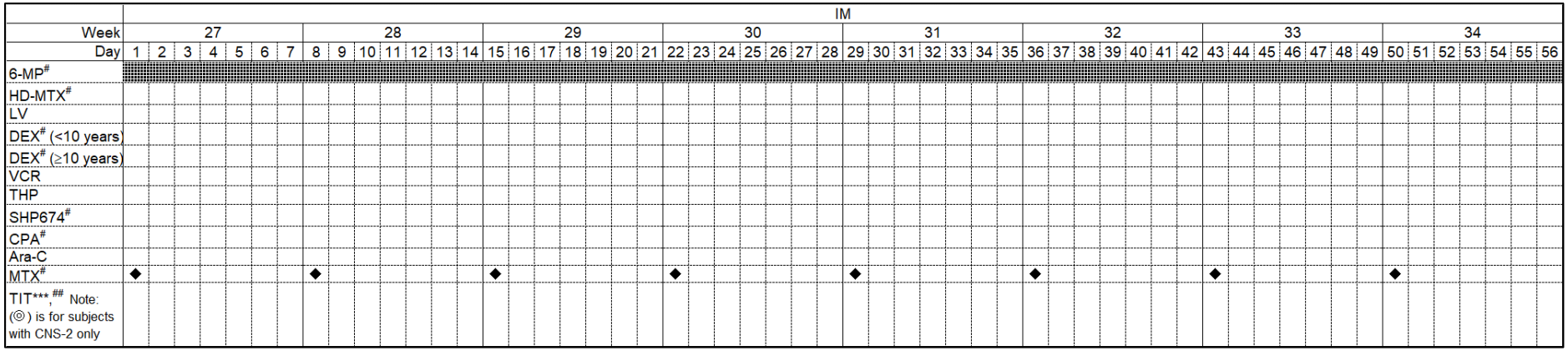
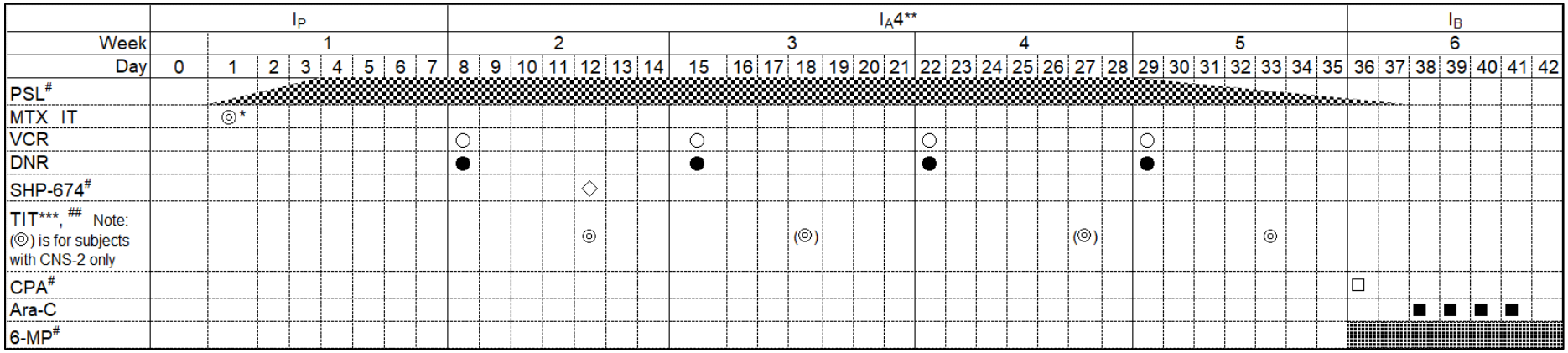


Table 7-1 Treatment Schedule for SR (Continued)

	IM														III																									
Week	35							36							37							38							39							40							41						
Day	57	58	59	60	61	62	63	64	65	66	67	68	69	70	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35
6-MP#																													▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒							
HD-MTX#																																																	
LV																																																	
DEX# (<10 years)															▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒							
DEX# (≥10 years)															▒	▒	▒	▒	▒	▒	▒								▒	▒	▒	▒	▒	▒	▒														
VCR															○							○																											
THP															▲							▲																											
SHP674#																◇																																	
CPA#																													□																				
Ara-C																															■	■	■	■				■	■	■	■							
MTX#																																																	
TIT***,## Note: (◎) is for subjects with CNS-2 only															(◎)																◎							◎												

Table 7-2 Treatment Schedule for IR



* If a subject cannot receive intrathecal MTX on Day 1 for a reason such as that the subject's initial visit falls on a weekend, the administration of MTX can be postponed until up to Day 4.
** I_A4 will be from Day 8 (Week 2) to the end of PSL administration on Day 37 (Week 6).
*** TIT is allowed to be performed within 3 days of the prescribed day if there is a social reason such as that the prescribed day falls on a weekend or holiday.
# To be provided by the Sponsor as an investigational product.
Only PSL will be provided by the Sponsor as an investigational product.

Each symbol represents the day of each drug administration.

Table 7-2 Treatment Schedule for IR (Continued)

	I_B																																		
Week	7							8							9							10							11						
Day	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77
PSL#																																			
MTX IT																																			
VCR																																			
DNR																																			
SHP-674#																																			
TIT***, ## Note: (◎) is for subjects with CNS-2 only			◎														◎																		
CPA#																						□													
Ara-C			■	■	■	■				■	■	■	■				■	■	■	■															
6-MP#	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓														

Table 7-2 Treatment Schedule for IR (Continued)

	M5																																																						
Week	12							13							14							15							16							17							18							19						
Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56
6-MP#	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓
HD-MTX#								◆24h														◆24h														◆24h														◆24h						
LV										↓↓↓														↓↓↓														↓↓↓														↓↓↓				
DEX# (<10 years)																																																								
DEX# (≥10 years)																																																								
VCR																																																								
THP																																																								
SHP674#																																																								
CPA#																																																								
Ara-C																																																								
MTX#																																																								
TIT##								◎														◎														◎														◎						

Table 7-2 Treatment Schedule for IR (Continued)

	M5														III																																		
Week	20							21							22							23							24							25							26						
Day	57	58	59	60	61	62	63	64	65	66	67	68	69	70	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35
6-MP#																													▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒							
HD-MTX#																																																	
LV																																																	
DEX# (<10 years)															▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒												
DEX# (≥10 years)															▒	▒	▒	▒	▒	▒	▒								▒	▒	▒	▒	▒	▒	▒														
VCR															○							○																											
THP															▲							▲																											
SHP674#																◇																																	
CPA#																													□																				
Ara-C																															■	■	■	■				■	■	■	■								
MTX#																																																	
TIT***, ## Note: (◎) is for subjects with CNS-2 only															(◎)																◎							◎											

Table 7-2 Treatment Schedule for IR (Continued)

	IM																																																						
Week	27							28							29							30							31							32							33							34						
Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56
6-MP#	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒
HD-MTX#																																																								
LV																																																								
DEX# (<10 years)																																																								
DEX# (≥10 years)																																																								
VCR																																																								
THP																																																								
SHP674#																																																								
CPA#																																																								
Ara-C																																																								
MTX#	◆							◆							◆							◆							◆							◆							◆							◆						
TIT***, ## Note: (◎) is for subjects with CNS-2 only	◎																												◎																											

Table 7-2 Treatment Schedule for IR (Continued)

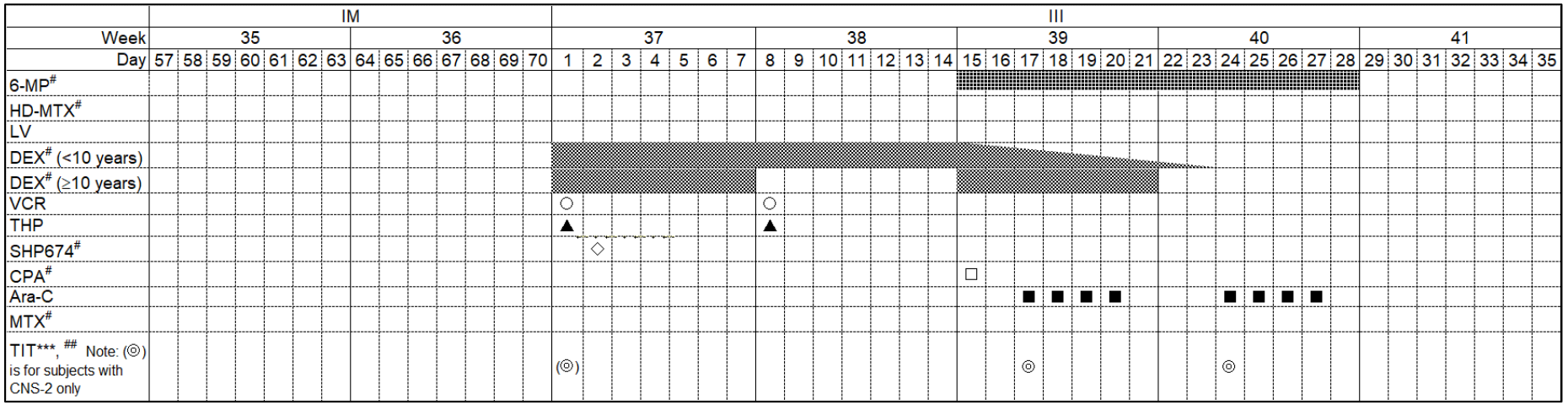


Table 7-3 Treatment Schedule for HR

	I_P								I_A4**																													I_B+L						
Week		1							2							3							4							5+2days							6						
Day	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42
PSL#		▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓					
MTX IT		◎*																																									
VCR									○							○							○							○													
DNR									●							●							●							●													
SHP674#													◇																										◇				
TIT***, ## Note: (◎) is for subjects with CNS-2 only													◎						(◎)									(◎)						◎									
CPA#																																					□						
Ara-C																																							■	■	■	■	
6-MP#																																					▓	▓	▓	▓	▓	▓	▓

* If a subject cannot receive intrathecal MTX on Day 1 for a reason such as that the subject's initial visit falls on a weekend, the administration of MTX can be postponed until up to Day 4.
** I_A4 will be from Day 8 (Week 2) to the end of PSL administration on Day 37 (Week 6).
*** TIT is allowed to be performed within 3 days of the prescribed day if there is a social reason such as that the prescribed day falls on a weekend or holiday.
# To be provided by the Sponsor as an investigational product.
Only PSL will be provided by the Sponsor as an investigational product.

Each symbol represents the day of each drug administration.

Table 7-3 Treatment Schedule for HR (Continued)

	I_B+L																																				
Week	7							8							9							10							11									
Day	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77		
PSL#																																					
MTX IT																																					
VCR																																					
DNR																																					
SHP674#																																					
TIT***, ## Note: (◎) is for subjects with CNS-2 only			◎														◎																					
CPA#																						□															
Ara-C			■	■	■	■				■	■	■	■				■	■	■	■																	
6-MP#	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒																

Table 7-3 Treatment Schedule for HR (Continued)

	HR3																				
Week	12							13							14						
Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
DEX#	▒	▒	▒	▒	▒																
HD-Ara-C	■■	■■																			
VP-16#			△	△△	△△																
VDS																					
DNR																					
HD-MTX#																					
LV																					
IFO#																					
VCR																					
CPA#																					
SHP674#						◇															
TIT***, ##					◎																

Table 7-3 Treatment Schedule for HR (Continued)

	HR2																					HR1																				
Week	15							16							17							18							19							20						
Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
DEX#	▒	▒	▒	▒	▒																	▒	▒	▒	▒	▒																
HD-Ara-C																										■■																
VP-16#																																										
VDS	▽					▽																																				
DNR					●24h																																					
HD-MTX#	◆24h																					◆24h																				
LV			↓↓↓																					↓↓↓																		
IFO#		▼	▼▼	▼▼																																						
VCR																						▽					▽															
CPA#																							□	□□	□□																	
SHP674#						◇																						◇														
TIT## Note: (◎) is for subjects with CNS-2 only	◎				(◎)																	◎																				

Table 7-3 Treatment Schedule for HR (Continued)

	III+L																																		
Week	21/31/41							22/32/42							23/33/43							24/34/44							25/35/45						
Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35
DEX# (<10 years)	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒												
DEX# (≥10 years)	▒	▒	▒	▒	▒	▒	▒								▒	▒	▒	▒	▒	▒	▒														
VCR	○							○																											
THP	▲							▲																											
SHP674#		◇																																	
CPA#															□																				
Ara-C																	■	■	■	■				■	■	■	■								
6-MP#															▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒	▒							
MTX#																																			
TIT***, ## Note (◎) is for subjects with CNS-2 only	(◎)																◎							◎											

Table 7-3 Treatment Schedule for HR (Continued)

	IM																																
Week	26/36							27/37							28/38							29/39							30/40						
Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35
DEX[#] (<10 years)																																			
DEX[#] (≥10 years)																																			
VCR																																			
THP																																			
SHP674[#]																																			
CPA[#]																																			
Ara-C																																			
6-MP[#]																																			
MTX[#]	◆							◆							◆							◆													
TIT***, ##																																			

7.1 Dose, Dosing Regimen, and Treatment Duration of SHP674

7.1.1 Dose and Dosing Regimen of SHP674

Subjects will receive a single IV dose of SHP674 at the following time points specified for each risk category:

SR: Total 3 doses

Remission induction therapy (I_A2), Day 12; re-induction therapy (III)*, Day 2

*Re-induction therapy (III) will be conducted twice.

IR: Total 3 doses

Remission induction therapy (I_A4), Day 12; re-induction therapy (III)*, Day 2

*Re-induction therapy (III) will be conducted twice.

HR: Total 8 doses

Remission induction therapy (I_A4), Day 12; early consolidation therapy (I_B+L), Day 38; consolidation therapy (HR3), Day 6; consolidation therapy (HR2), Day 6; consolidation therapy (HR1), Day 7; re-induction therapy (III+L)*, Day 2

*Re-induction therapy (III+L) will be conducted 3 times.

For the outline of the treatment schedule, see Table 7-1, Table 7-2, and Table 7-3.

The dose of SHP674 will be determined as below according to the body surface area (BSA) of each subject. No dose increase or reduction will be conducted.

- BSA ≥0.6 m^2: 2500 IU/m^2
- BSA <0.6 m^2: 82.5 IU/kg

When SHP674 is used, the following information should be entered into the eCRF:

- Date and time of administration
- Dose administered

7.1.1.1 Formula for Calculation of Body Surface Area (BSA)

The BSA will be calculated based on the height and weight measured on the start day of each treatment phase (including Day 8 of remission induction therapy [I_A2/I_A4] and Day 36 of early consolidation therapy [I_B/I_B+L]), according to the following formula. Height and weight measured within 7 days (3 days for Pre-treatment Phase Day 1) before the prescribed day will be acceptable.

$$\text{BSA} = \sqrt{(\text{Height [cm]} \times \text{Weight [kg]}/3600)}$$

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 cm)

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).

7.1.2 Rationale for Dose and Dosing Regimen of SHP674

Treatment in this study will be based on the regimen used in Study ALL-B12.[17] Native L-asparaginase in the treatment regimen of Study ALL-B12 will be replaced by SHP674; SHP674 will be administered on the day of the first dose of native L-asparaginase in each treatment phase. SHP674 is recommended to be administered at least 12 hours after vincristine administration because of potential drug-drug interactions. Thus, if vincristine administration is scheduled on the same day as SHP674, the administration of SHP674 will be postponed by 1 day (see Investigator's Brochure for SHP674).

It is considered that there are generally no ethnic differences in the PK of SHP674, since it is a protein product and not affected by polymorphic drug-metabolizing enzymes. There are no data comparing the pharmacokinetics of SHP674 in Japanese subjects with those in foreign subjects; however, a population pharmacokinetic analysis was conducted on data from 144 subjects (Asian subjects, 9; non-Asian subjects, 135 subjects) who were enrolled in Study AALL07P4, DFCI 11-001, or CCG-1962 and received SHP674. As a result, there was no difference in the pharmacokinetic profile of SHP674 between Asian subjects and non-Asian subjects. On the basis of the results mentioned above, the dose of SHP674 in this study will be the same as that in Europe.

7.2 Concomitant Medications and Therapies

The following information will be entered into the eCRF if any drug or therapy other than SHP674 or the backbone therapy drugs specified in Section 7.2.1 was received by a subject during the period from the day of informed consent to the day of the end-of-study or early termination assessment or 30 days after the last dose of investigational product, whichever comes later:

- Name of drug (non-proprietary name) or therapy
- Start date and end date of treatment
- Route of administration
- Reason for use

As a general rule, non-proprietary name should be provided as the name of drug, but brand name is acceptable for combination products.

7.2.1 Backbone Therapy Drugs Used in This Study

The drugs for combination chemotherapy other than SHP674 will be administered according to the regimens used in Study ALL-B12. The backbone therapy drugs used in this study are as listed below. For the drugs provided by the Sponsor for investigational use, see Section 6.1.

Ifosfamide (IFO)	Brand name: Ifomide®
Cyclophosphamide (CPA)	Brand name: Endoxan®
Methotrexate (MTX)	Brand name: Methotrexate®
Cytarabine (Ara-C)	Brand name: Cylocide®, Cylocide®N
Mercaptopurine hydrate (6-MP)	Brand name: Leukerin®
Etoposide (VP-16)	Brand name: Lastet®
Daunorubicin (DNR)	Brand name: Daunomycin®
Pirarubicin hydrochloride (THP)	Brand name: Therarubicin®, Pinorubin®
Vincristine (VCR)	Brand name: Oncovin ®
Vindesine (VDS)	Brand name: Fildesin®

Dexamethasone (DEX)	Brand name: Decadron®
Prednisolone (PSL)	Brand name: Predonine®, Prednisolone Powder 1%
Calcium Folinate (LV)	Brand name: Leucovorin®

When any of the backbone therapy drugs listed in this section is used, the following information should be entered into the eCRF:

- Date and time of administration or duration of administration
- Dose*
- Route of administration
- Reason for change in treatment

* If a dose of a powder drug is not completely taken, 50% of the scheduled dose will be entered into the eCRF as the amount taken, regardless of the actual amount of the remaining powder.

7.2.1.1 Doses of Backbone Therapy Drugs Used in This Study

For the formula for calculation of BSA, see Section 7.1.1.1. The BSA will be calculated based on the height and weight measured on the start day of each treatment phase (including Day 8 of remission induction therapy [I_A2/I_A4]) and Day 36 of early consolidation therapy [I_B/I_B+L]), according to the formula provided in Section 7.1.1.1. Height and weight are allowed to be measured within 7 days (3 days for Pre-treatment Phase Day 1) before the prescribed day.

If a subject's body weight exceeds 30% of the ideal body weight,[19] the dose will be calculated using the value that is 1.3-fold the ideal body weight of the subject. The ideal body weight in subjects ≥18 years will be calculated according to the formula "height (m) × height (m) × 22." If the subject's body weight exceeds 30% of the ideal body weight, the dose will be calculated using the value that is 1.3-fold the ideal body weight of the subject. Note that these rules are not applied to SHP674.

The dose of backbone therapy drugs other than VCR will be calculated to two significant figures. The dose of VCR will be rounded off to two decimal places if the calculated dose is <1 mg and will be rounded up to two significant figures if the calculated dose is ≥1 mg. This rule does not apply to SHP674. For backbone therapy drugs with age-based dosage rules, the dose will be determined by age at the start date of each treatment phase.

7.2.2 Outline of Each Treatment Phase

As a general rule, statements in this section should be followed regarding the dose and dosing regimen of each backbone therapy drug.

7.2.2.1 Pre-treatment Phase (I_P)

Before determining the risk category, all subjects will receive an intrathecal dose of methotrexate (MTX) alone and start treatment with oral (or IV) prednisolone (PSL) on Day 1 of the pre-treatment phase. PSL will be administered divided into 3 doses per day. If a subject cannot receive intrathecal MTX (MTX IT) on Day 1 for a reason such as that the subject's initial visit falls on a weekend, the administration of MTX can be postponed until up to Day 4. The dose of MTX will be 8 mg for subjects 1 to <2 years, 10 mg for subjects 2 to <3 years, and 12 mg for subjects ≥3 years. The oral (or IV) administration of PSL will be started at 15 mg/m^2/day. The dose will then be titrated to 30 mg/m^2/day on Day 2 and 60 mg/m^2/day by Day 4 or 5. PSL will be administered for 7 days. The total dosage of PSL for 7 days will be ≥210 mg/m^2.

Points to note and criteria for changes in treatment must be followed during the pre-treatment phase (see Section 7.4.1).

Table 7.2.2.1-1 Dosing Schedule for I_P

	I_P							
Week		1						
Day	0	1	2	3	4	5	6	7
PSL#								
MTX IT		◎*						

* If a subject cannot receive intrathecal MTX on Day 1 for a reason such as that the subject's initial visit falls on a weekend, the administration of MTX can be postponed until up to Day 4.
# To be provided by the Sponsor as an investigational product.

Table 7.2.2.1-2 Route of Administration, Dose, and Days of Administration of Drugs Used in I_P

Drug	Administration
PSL#	Day 1 to Day7 (ascending dose) Day 1, 15 mg/m^2; Day 2, 30 mg/m^2; The dose will be increased to 60 mg/m^2 by Day 4 or Day 5. Oral or IV administration in 3 doses per day
MTX IT	Day 1 (*If a subject cannot receive intrathecal MTX on Day 1 for a reason such as that the subject's initial visit falls on a weekend, the administration of MTX can be postponed until up to Day 4. The dose of MTX will be 8 mg for subjects 1 to <2 years, 10 mg for subjects 2 to <3 years, and 12 mg for subjects ≥3 years.)

To be provided by the Sponsor as an investigational product.

7.2.2.2 Remission Induction Therapy (I_A2/I_A4)

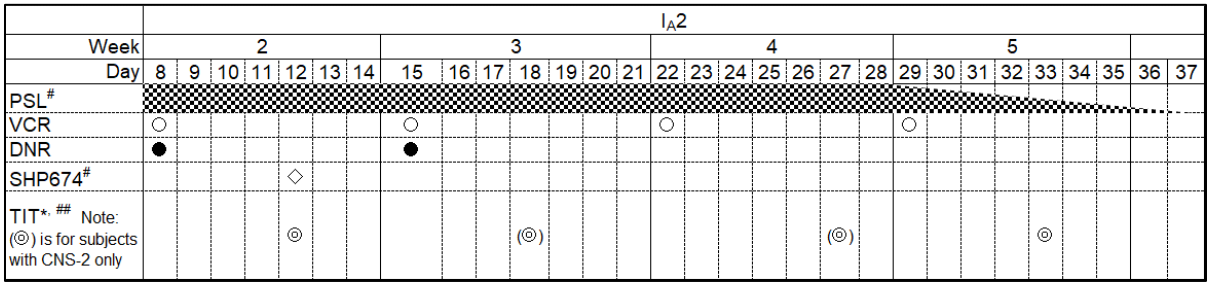
7.2.2.2.1 I_A2

I_A2 is remission induction therapy for SR. Vincristine (VCR) will be administered intravenously at 1.5 mg/m^2 (maximum 2 mg) on Days 8, 15, 22, and 29. PSL will be administered orally (or intravenously) at 60 mg/m^2/day from Day 8 to Day 28, divided into 3 doses per day. The dose of PSL will be decreased by half every 3 days from Day 29, and the administration of PSL will be completed on Day 37. Day 36 and Day 37 of I_A2 will overlap with early consolidation therapy. Daunorubicin (DNR) will be administered intravenously for 60±15 minutes at 30 mg/m^2 on Days 8 and 15. In addition, MTX, cytarabine (Ara-C), and PSL will be administered intrathecally on Days 12 and 33 (triple intrathecal therapy [TIT]). Subjects with CNS-2 status will receive additional doses of TIT on Days 18 and 27. The doses of MTX, Ara-C, and PSL will be determined according to Table 7.2.2.2.1-1. SHP674 will be administered intravenously for 90±30 minutes at 2500 IU/m^2 (if body surface area is ≥0.6 m^2) or at 82.5 IU/kg (if body surface area is <0.6 m^2) on Day 12. Note that the risk category of subjects may be changed in remission induction therapy (see Section 3.1.3.1).

Table 7.2.2.2.1-1 Doses of Drugs for TIT

Age	1 to <2 years	2 to <3 years	≥3 years
MTX (mg)	8	10	12
Ara-C (mg)	20	26	30
PSL (mg)	6	8	10

Table 7.2.2.2.1-2 Dosing Schedule for I_A2



* TIT is allowed to be performed within 3 days of the prescribed day if there is a social reason such as that the prescribed day falls on a weekend or holiday.
# To be provided by the Sponsor as an investigational product.
Only PSL will be provided by the Sponsor as an investigational product.

Table 7.2.2.4.3.1-3 Route of Administration, Dose, and Days of Administration of Drugs Used in IA2

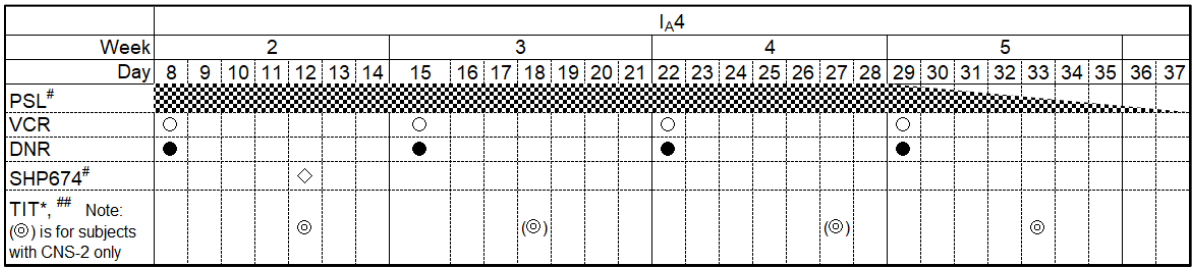
Drug	Route of Administration	Dose	Days of Administration
PSL#	PO or IV in 3 doses	60 mg/m^2	Day 8 to Day 28
PSL#	PO or IV in 3 doses	30→15→7.5 mg/m^2	Day 29 to Day 37 (dose tapering for 9 days)
VCR	IV	1.5 mg/m^2 (up to 2 mg)	Days 8, 15, 22, and 29
DNR	IV (60±15 minutes)	30 mg/m^2	Day 8, 15
SHP674#	IV (90±30 minutes)	BSA ≥0.6 m^2: 2500 IU/m^2 BSA <0.6 m^2: 82.5 IU/kg	Day 12
TIT*: MTX, Ara-C, PSL#	IT	See Table 7.2.2.2.1-1	Days 12 and 33; subjects with CNS-2 will receive additional doses on Days 18 and 27.

* TIT is allowed to be performed within 3 days of the prescribed day if there is a social reason such as that the prescribed day falls on a weekend or holiday.
# To be provided by the Sponsor as an investigational product.

7.2.2.2.2 I_A4

I_A4 is remission induction therapy for IR and HR. VCR will be administered intravenously at 1.5 mg/m^2 (maximum 2 mg) on Days 8, 15, 22, and 29. PSL will be administered orally (or intravenously) at 60 mg/m^2/day from Day 8 to Day 28, divided into 3 doses per day. The dose of PSL will be decreased by half every 3 days from Day 29, and the administration of PSL will be completed on Day 37. Day 36 and Day 37 of I_A4 will overlap with early consolidation therapy. DNR will be administered intravenously for 60±15 minutes at 30 mg/m^2 on Days 8, 15, 22 and 29. In addition, MTX, Ara-C, and PSL will be administered intrathecally on Days 12 and 33 (TIT). Subjects with CNS-2 status will receive additional doses of TIT on Days 18 and 27. The doses of MTX, Ara-C, and PSL will be determined according to Table 7.2.2.2.1-1. TIT is allowed to be performed within 3 days of the prescribed dose if there is a social reason such as that the prescribed day falls on a weekend or holiday. SHP674 will be administered intravenously for 90±30 minutes at 2500 IU/m^2 (if body surface area is ≥0.6 m^2) or at 82.5 IU/kg (if body surface area is <0.6 m^2) on Day 12. Note that the risk category of subjects may be changed in I_A4 (see Section 3.1.3.1).

Table 7.2.2.2.2-1 Dosing Schedule for I_A4



* TIT is allowed to be performed within 3 days of the prescribed day if there is a social reason such as that the prescribed day falls on a weekend or holiday.

To be provided by the Sponsor as an investigational product.

Only PSL will be provided by the Sponsor as an investigational product.

Table 7.2.2.2.2-2 Route of Administration, Dose, and Days of Administration of Drugs Used in I_A4

Drug	Route of Administration	Dose	Days of Administration
PSL#	PO or IV in 3 doses	60 mg/m^2	Day 8 to Day 28
PSL#	PO or IV in 3 doses	30→15→7.5 mg/m^2	Day 29 to Day 37 (dose tapering for 9 days)
VCR	IV	1.5 mg/m2 (up to 2 mg)	Days 8, 15, 22, 29
DNR	IV (60±15 minutes)	30 mg/m^2	Days 8, 15, 22, 29
SHP674#	IV (90±30 minutes)	BSA ≥0.6 m^2: 2500 IU/m^2 BSA <0.6 m^2: 82.5 IU/kg	Day 12
TIT*: MTX, Ara-C, PSL#	IT	See Table 7.2.2.2.1-1	Days 12 and 33; subjects with CNS-2 will receive additional doses on Days 18 and 27.

* TIT is allowed to be performed within 3 days of the prescribed day if there is a social reason such as that the prescribed day falls on a weekend or holiday.

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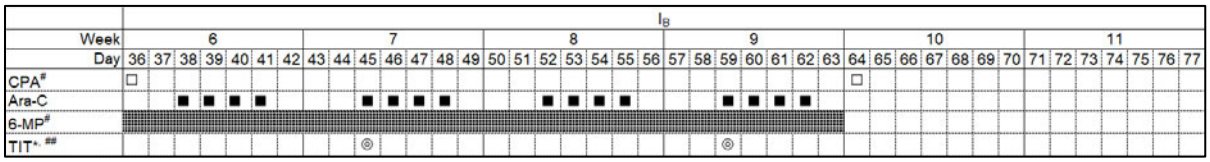
7.2.2.3 Early Consolidation Therapy (I_B/I_B+L)

7.2.2.3.1 I_B

I_B is early consolidation therapy for SR and IR. Cyclophosphamide (CPA) will be administered intravenously for 60±15 minutes at 1000 mg/m^2 on Days 36 and 64. The criteria for starting treatment with CPA must be followed on Day 64 (see Section 0). 6-Mercaptopurine (6-MP) will be administered orally at 60 mg/m^2 once daily at bedtime from Day 36 to Day 63. Ara-C will be administered intravenously by rapid injection or for ≤15 minutes once daily on Days 38 to 41, Days 45 to 48, Days 52 to 55, and Days 59 to 62. The criteria for starting treatment with Ara-C must be followed (see Section 0). In addition, Ara-C, MTX, and PSL will be administered intrathecally on Days 45 and 59 (TIT). The dose will be determined according to Table 7.2.2.2.1-1. TIT is allowed to be performed within 3 days of the prescribed day if there is a social reason such as that the prescribed day falls on a weekend or holiday. Points to note and criteria for changes in treatment must be followed during early consolidation therapy (see Section 7.4.3).

Table 7.2.2.3.1-1 Dosing Schedule for I_B



* TIT is allowed to be performed within 3 days of the prescribed day if there is a social reason such as that the prescribed day falls on a weekend or holiday.
# To be provided by the Sponsor as an investigational product.
Only PSL will be provided by the Sponsor as an investigational product.

Table 7.2.2.3.1-2 Route of Administration, Dose, and Days of Administration of Drugs Used in I_B

Drug	Route of Administration	Dose	Days of Administration
CPA#	IV (60±15 minutes)	1000 mg/m^2	Days 36 and 64
Ara-C	IV (by rapid injection or for ≤15 minutes)	75 mg/m^2	Day 38 to Day 41, Day 45 to Day 48, Day 52 to Day 55, Day 59 to Day 62
6-MP#	PO in one dose at bedtime	60 mg/m^2 (The dose will be adjusted according to the results of NUDT15 codon 139 polymorphism analysis. See Section 7.2.3-(7).)	Day 36 to Day 63
TIT*: MTX, Ara-C, PSL#	IT	See Table 7.2.2.2.1-1.	Day 45 and Day 59

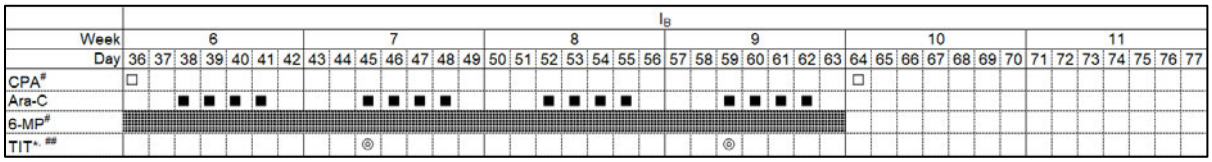
* TIT is allowed to be performed within 3 days of the prescribed day if there is a social reason such as that the prescribed day falls on a weekend or holiday.
# To be provided by the Sponsor as an investigational product.

7.2.2.3.2 I_B+L

I_B+L is early consolidation therapy for HR. CPA will be administered intravenously for 60±15 minutes at 1000 mg/m^2 on Days 36 and 64. The criteria for starting treatment with CPA must be followed on Day 64 (see Section 7.2.3). 6-MP will be administered orally at 60 mg/m^2 once daily at bedtime from Day 36 to Day 63. Ara-C will be administered intravenously by rapid injection or for ≤15 minutes once daily on Days 38 to 41, Days 45 to 48, Days 52 to 55, and Days 59 to 62. The criteria for starting treatment with Ara-C must be followed (see Section 7.2.3). In addition, MTX, Ara-C, and PSL will be administered intrathecally on Days 45 and 59 (TIT). The dose will be determined according to Table 7.2.2.2.1-1. TIT is allowed to be performed within 3 days of the prescribed day if there is a social reason such as that the prescribed day falls on a weekend or holiday.

SHP674 will be administered intravenously for 90±30 minutes at 2500 IU/m^2 (if body surface area is ≥0.6 m^2) or at 82.5 IU/kg (if body surface area is <0.6 m^2) on Day 38. Points to note and criteria for changes in treatment must be followed during early consolidation therapy (see Section 7.4.3).

Table 7.2.2.3.2-1 Dosing Schedule for I_B+L



* TIT is allowed to be performed within 3 days of the prescribed day if there is a social reason such as that the prescribed day falls on a weekend or holiday.
# To be provided by the Sponsor as an investigational product.
Only PSL will be provided by the Sponsor as an investigational product.

Table 7.2.2.3.2-2 Route of Administration, Dose, and Days of Administration of Drugs Used in I_B+L

Drug	Route of Administration	Dose	Days of Administration
CPA#	IV (60±15 minutes)	1000 mg/m^2	Days 36 and 64
Ara-C	IV (by rapid injection or for ≤15 minutes)	75 mg/m^2	Day 38 to Day 41, Day 45 to Day 48, Day 52 to Day 55, Day 59 to Day 62
6-MP#	PO in one dose at bedtime	60 mg/m^2 (The dose will be adjusted according to the results of NUDT15 codon 139 polymorphism analysis. See Section 7.2.3-(7).)	Day 36 to Day 63
SHP674#	IV (90±30 minutes)	BSA ≥0.6 m^2: 2500 IU/m^2 BSA <0.6 m^2: 82.5 IU/kg	Day 38
TIT*: MTX, Ara-C, PSL#	IT	See Table 7.2.2.2.1-1.	Days 45 and 59

* TIT is allowed to be performed within 3 days of the prescribed day if there is a social reason such as that the prescribed day falls on a weekend or holiday.
# To be provided by the Sponsor as an investigational product.

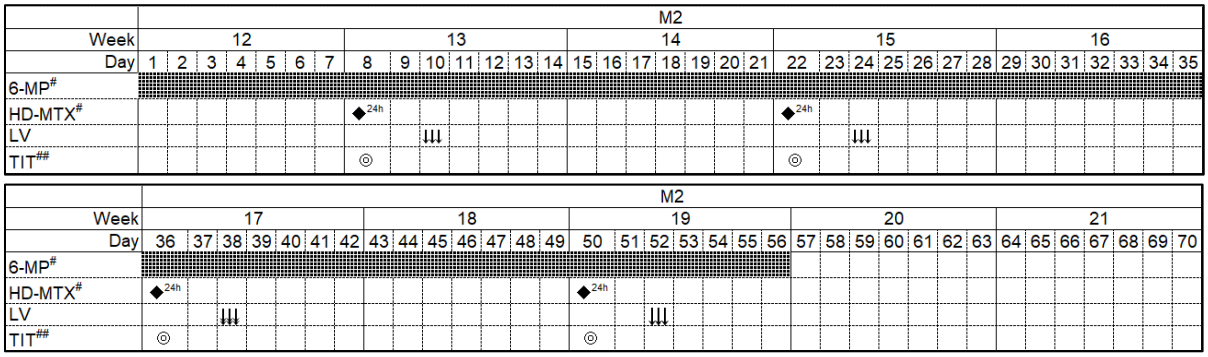
7.2.2.4 Consolidation Therapy (M2/M5/HR3→HR2→HR1)

7.2.2.4.1 M2

M2 is consolidation therapy for SR. The start day of 6-MP administration will be regarded as Day 1. High-dose methotrexate (HD-MTX) will be administered on Days 8, 22, 36, and 50 (total 4 doses). The following are the details of HD-MTX administration.

HD-MTX will be administered intravenously at 2 g/m^2, 10% (0.2 g/m^2) of which will be administered for 0.5 hours, and the remaining 90% (1.8 g/m^2) will be administered for 23.5 hours (total 24±2 hours). Leucovorin (LV) rescue will be performed after HD-MTX administration. The details of the LV rescue regimen and points to note for HD-MTX administration are described in **Dosing Criteria and Points to Note for HD-MTX Administration**. 6-MP will be administered orally at 25 mg/m^2 once daily at bedtime from Day 1 to Day 56. In addition, MTX, Ara-C, and PSL will be administered intrathecally during HD-MTX administration on Days 8, 22, 36, and 50 (TIT). The intrathecal administration of these drugs should be performed at least 30 minutes after the start of HD-MTX but before the end of HD-MTX. The doses of the intrathecal drugs will be determined according to Table 7.2.2.2.1-1. Points to note and criteria for changes in treatment must be followed during consolidation therapy (see Section 7.4.4).

Table 7.2.2.4.1-1 Dosing Schedule for M2



To be provided by the Sponsor as an investigational product.
Only PSL will be provided by the Sponsor as an investigational product.

Table 7.2.2.4.1-2 Route of Administration, Dose, and Days of Administration of Drugs Used in M2

Drug	Route of Administration	Dose	Days of Administration
6-MP#	PO in one dose at bedtime	25 mg/m^2 (The dose will be adjusted according to the results of NUDT15 codon 139 polymorphism analysis. See Section 7.2.3-(7).)	Day 1 to Day 56
HD-MTX#	IV (24±2 hours) For each of 4 doses, administer 10% for 0.5 hours and the remaining 90% for 23.5 hours by intravenous infusion.	2 g/m^2	Days 8, 22, 36, and 50
LV rescue	IV	15 mg/m^2	42, 48, and 54 hours after the start of MTX administration (see “Detailed procedure for LV rescue” in Section 7.2.3)
TIT: MTX, Ara-C, PSL#	IT	See Table 7.2.2.2.1-1.	Days 8, 22, 36, and 50 Complete administration at least 30 minutes after the start of HD-MTX administration but before the end of HD-MTX administration

To be provided by the Sponsor as an investigational product.

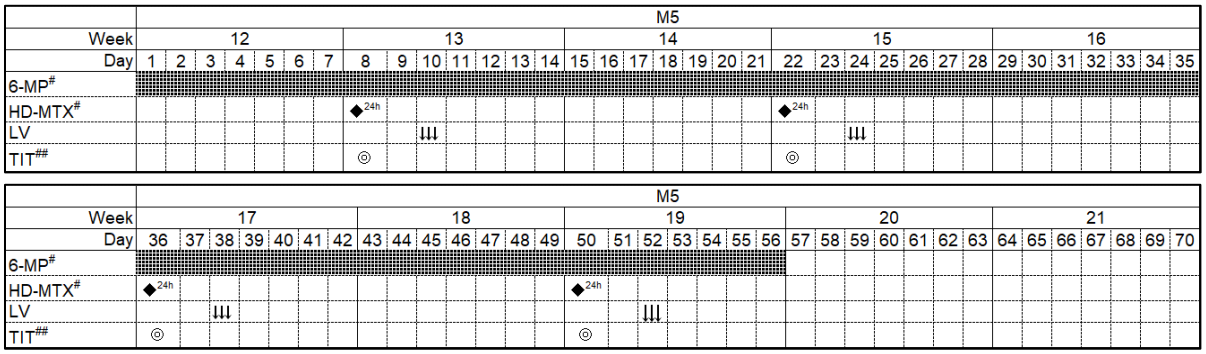
7.2.2.4.2 M5

M5 is consolidation therapy for IR. The start day of 6-MP administration will be regarded as Day 1. HD-MTX will be administered on Days 8, 22, 36, and 50 (total 4 doses). The following are the details of HD-MTX administration.

HD-MTX will be administered intravenously at 5 g/m^2, 10% (0.5 g/m^2) of which will be administered for 0.5 hours, and the remaining 90% (4.5 g/m^2) will be administered for 23.5 hours (total 24±2 hours). LV rescue will be performed after HD-MTX administration. The details of the LV rescue regimen and points to note for HD-MTX administration are described in **Dosing Criteria and Points to Note for HD-MTX Administration**. 6-MP will be administered orally at 25 mg/m^2 once daily at bedtime from Day 1 to Day 56. In addition, MTX, Ara-C, and PSL will be administered intrathecally during HD-MTX administration on Days 8, 22, 36, and 50 (TIT). The intrathecal administration of these drugs should be performed at least 30 minutes after the start of HD-MTX but before the end of HD-MTX. The doses of the intrathecal drugs

are determined according to Table 7.2.2.2.1-1. Points to note and criteria for changes in treatment must be followed during consolidation therapy (see Section 7.4.4).

Table 7.2.2.4.2-1 Dosing Schedule for M5



To be provided by the Sponsor as an investigational product.
Only PSL will be provided by the Sponsor as an investigational product.

Table 7.2.2.4.2-2 Route of Administration, Dose, and Days of Administration of Drugs Used in M5

Drug	Route of Administration	Dose	Days of Administration
6-MP#	PO in one dose at bedtime	25 mg/m^2 (The dose will be adjusted according to the results of NUDT15 codon 139 polymorphism analysis. See Section 7.2.3-(7).)	Day 1 to Day 56
HD-MTX#	IV (24±2 hours) For each of 4 doses, administer 10% for 0.5 hours and the remaining 90% for 23.5 hours by intravenous infusion.	5 g/m^2	Days 8, 22, 36, and 50
LV rescue	IV	15 mg/m^2	42, 48, and 54 hours after the start of MTX administration (see "Detailed procedure for LV rescue" in Section 7.2.3)
TIT: MTX, Ara-C, PSL#	IT	See Table 7.2.2.2.1-1.	Days 8, 22, 36, and 50 Complete administration at least 30 minutes after the start of HD-MTX administration but before the end of HD-MTX administration

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7.2.2.4.3 HR3, HR2, and HR1

HR3, HR2, and HR1 are blocks of consolidation therapy for HR. Subjects will receive HR3, HR2, and HR1 sequentially in this order.

7.2.2.4.3.1 HR3

The start day of the administration of DEX or HD-Ara-C, whichever is administered first, will be regarded as Day 1. Dexamethasone (DEX) will be administered orally (or intravenously) at 20 mg/m^2/day divided into 3 doses per day from Day 1 to Day 5. Ara-C will be administered intravenously a total of 4

times every 12 hours from Day 1 to Day 2 (high-dose [HD] Ara-C). The dose of Ara-C will be 2000 mg/m^2; the total dose administered will be 8000 mg/m^2. Ara-C will be administered intravenously for 180±15 minutes per dose. Etoposide (VP-16) will be administered intravenously a total of 5 times every 12 hours from Day 3 to Day 5 (the administration of the first dose on Day 3 is recommended to be started in the afternoon). VP-16 will be administered intravenously for 60±15 minutes at 100 mg/m^2. In addition, MTX, Ara-C, and PSL will be administered intrathecally on Day 5 (TIT). The doses of the intrathecal drugs are determined according to Table 7.2.2.2.1-1. TIT is allowed to be performed within 3 days of the prescribed day if there is a social reason such as that the prescribed day falls on a weekend or holiday. SHP674 will be administered intravenously for 90±30 minutes at 2500 IU/m^2 (if body surface area is ≥0.6 m^2) or at 82.5 IU/kg (if body surface area is <0.6 m^2) on Day 6.

Table 7.2.2.4.3.1-1 Dosing Schedule for HR3

	HR3																				
Week	12							13							14						
Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
DEX#	▒	▒	▒	▒	▒																
HD-Ara-C	■■	■■																			
VP-16#			△	△△	△△																
SHP674#						◇															
TIT*, ##					◎																

* TIT is allowed to be performed within 3 days of the prescribed day if there is a social reason such as that the prescribed day falls on a weekend or holiday.
# To be provided by the Sponsor as an investigational product.
Only PSL will be provided by the Sponsor as an investigational product.

Table 7.2.2.4.3.1-2 Route of Administration, Dose, and Days of Administration of Drugs Used in HR3

Drug	Route of Administration	Dose	Days of Administration
DEX#	PO or IV in 3 doses	20 mg/m^2	Day 1 to Day 5
HD-Ara-C	IV (180±15 minutes)	2000 mg/m^2	Day 1 to Day 2 4 doses every 12 hours
VP-16#	IV (60±15 minutes)	100 mg/m^2	Day 3 to Day 5 5 (2+2+1) doses every 12 hours (first dose on Day 3 is recommended to be started in the afternoon)
SHP674#	IV (90±30 minutes)	BSA ≥0.6 m^2: 2500 IU/m^2 BSA <0.6 m^2: 82.5 IU/kg	Day 6
TIT*: MTX, Ara-C, PSL#	IT	See Table 7.2.2.2.1-1.	Day 5

* TIT is allowed to be performed within 3 days of the prescribed day if there is a social reason such as that the prescribed day falls on a weekend or holiday.
# To be provided by the Sponsor as an investigational product.

7.2.2.4.3.2 HR2

The start day of the administration of DEX, VDS, HD-MTX, or TIT, whichever is administered first, will be regarded as Day 1. DEX will be administered orally (or intravenously) at 20 mg/m^2/day divided into 3 doses per day from Day 1 to Day 5. Vindesine (VDS) will be administered intravenously at 3 mg/m^2 (maximum 5 mg) on Days 1 and 6. HD-MTX will be administered on Day 1. The following are the details of HD-MTX administration.

HD-MTX will be administered intravenously at 5 g/m^2, 10% (0.5 g/m^2) of which will be administered for 0.5 hours, and the remaining 90% (4.5 g/m^2) will be administered for 23.5 hours (total 24±2 hours). LV rescue will be performed after HD-MTX administration. The details of the LV rescue regimen and points to note for HD-MTX administration are described in **Dosing Criteria and Points to Note for HD-MTX Administration**. Ifosfamide (IFO) will be administered intravenously a total of 5 times every 12 hours from Day 2 to Day 4. The dose of IFO will be 800 mg/m^2; the total dose administered will be 4 g/m^2. IFO will be administered intravenously for 60±15 minutes per dose. DNR will be administered intravenously for 24±2 hours at 30 mg/m^2 on Day 5. In addition, MTX, Ara-C, and PSL will be administered intrathecally on Day 1 (TIT). Subjects with CNS-2 status will receive an additional dose of TIT on Day 5). The doses of the intrathecal drugs are determined according to Table 7.2.2.2.1-1. SHP674 will be administered intravenously for 90±30 minutes at 2500 IU/m^2 (if body surface area is ≥0.6 m^2) or at 82.5 IU/kg (if body surface area is <0.6 m^2) on Day 6.

Table 7.2.2.4.3.2-1 Dosing Schedule for HR2

	HR2																				
Week	15							16							17						
Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
DEX#	▒	▒	▒	▒	▒																
VDS	▽					▽															
DNR					● 24h																
HD-MTX#	◆ 24h																				
LV			⇊																		
IFO#		▼	▼▼	▼▼																	
SHP674#						◇															
TIT## Note: (◎) is for subjects with CNS-2 only	◎				(◎)																

To be provided by the Sponsor as an investigational product.
Only PSL will be provided by the Sponsor as an investigational product.

Table 7.2.2.4.3.2-2 Route of Administration, Dose, and Days of Administration of Drugs Used in HR2

Dose	Route of Administration	Dose	Days of Administration
DEX#	PO or IV in 3 doses	20 mg/m^2	Day 1 to Day 5
VDS	IV	3 mg/m^2 (up to 5 mg)	Days 1 and 6
DNR	IV (24±2 hours)	30 mg/m^2	Day 5
HD-MTX#	IV (24±2 hours) Administer 10% of the dose for 0.5 hours and the remaining 90% for 23.5 hours by intravenous infusion.	5 g/m^2	Day 1
LV rescue	IV	15 mg/m^2	42, 48, 54 hours after the start of MTX administration (see "Detailed procedure for LV rescue" in Section 7.2.3)
IFO*,#	IV (60±15 minutes)	800 mg/m^2	Administer 5 doses of IFO every 12 hours from Day 2 to Day 4, using mesna concomitantly.
SHP674#	IV (90±30 minutes)	BSA ≥0.6 m^2: 2500 IU/m^2 BSA <0.6 m^2: 82.5 IU/kg	Day 6
TIT: MTX, Ara-C, PSL#	IT	See Table 7.2.2.2.1-1.	Day 1 Subjects with CNS-2 will receive an additional dose on Day 5.

* When administering IFO, supportive care should be considered based on the following procedure used in the regimen of Study ALL-B12 IFO:
For prevention of hemorrhagic cystitis, adequate diuresis should be maintained with 3000 mL/m^2 per day of fluid replacement and a diuretic drug such as Lasix®. It is also recommended that mesna (Uromitexan®) be administered intravenously at a dose of 160 mg/m^2 immediately before IFO administration and 4 and 8 hours after the start of IFO administration.
To be provided by the Sponsor as an investigational product.

7.2.2.4.3.3 HR1

The start day of the administration of DEX, HD-MTX, VCR or TIT, whichever is administered first, will be regarded as Day 1. DEX will be administered orally (or intravenously) at 20 mg/m^2/day divided into 3 doses per day from Day 1 to Day 5. VCR will be administered intravenously at 1.5 mg/m^2

(maximum 2 mg) on Days 1 and 6. HD-MTX will be administered on Day 1. The following are the details of HD-MTX administration.

HD-MTX will be administered intravenously at 5 g/m^2, 10% (0.5 g/m^2) of which will be administered for 0.5 hours, and the remaining 90% (4.5 g/m^2) will be administered for 23.5 hours (total 24±2 hours). LV rescue will be performed after HD-MTX administration. The details of the LV rescue regimen and points to note in administering HD-MTX are described in **Dosing Criteria and Points to Note for HD-MTX Administration**. Ara-C will be administered intravenously twice every 12 hours on Day 5. The dose of Ara-C will be 2000 mg/m^2; the total dose administered will be 4000 mg/m^2. Ara-C will be administered intravenously for 180±15 minutes per dose.

CPA will be administered intravenously a total of 5 times every 12 hours from Day 2 to Day 4 (the administration of the first dose on Day 2 is recommended to be started in the afternoon). The dose of CPA will be 200 mg/m^2; the total dose administered will be 1 g/m^2. CPA will be administered intravenously for 60±15 minutes per dose. In addition, MTX, Ara-C, and PSL will be administered intrathecally on Day 1 (TIT). The doses of the intrathecal drugs are determined according to Table 7.2.2.2.1-1. SHP674 will be administered intravenously for 90±30 minutes at 2500 IU/m^2 (if body surface area is ≥0.6 m^2) or at 82.5 IU/kg (if body surface area is <0.6 m^2) on Day 7.

Table 7.2.2.4.3.3-1 Dosing Schedule for HR1

	HR1																				
Week	18							19							20						
Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
DEX#	▒	▒	▒	▒	▒																
HD-Ara-C					■■																
HD-MTX#	◆24h																				
LV			⇊⇊																		
VCR	▽					▽															
CPA#		□	□□	□□																	
SHP674#							◇														
TIT##	◎																				

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Only PSL will be provided by the Sponsor as an investigational product.

Table 7.2.2.4.3.3-2 Route of Administration, Dose, and Days of Administration of Drugs Used in HR1

Drug	Route of Administration	Dose	Days of Administration
DEX#	PO or IV in 3 doses	20 mg/m^2	Day 1 to Day 5
VCR	IV	1.5 mg/m^2 (up to 2 mg)	Days 1 and 6
HD-MTX#	IV (24±2 hours) Administer 10% of the dose for 0.5 hours and the remaining 90% for 23.5 hours by intravenous infusion.	5 g/m^2	Day 1
LV rescue	IV	15 mg/m^2	42, 48, and 54 hours after the start of MTX administration
HD-Ara-C	IV (180±15 minutes)	2000 mg/m^2	Day 5: Administer 2 doses every 12 hours
CPA#	IV (60±15 minutes)	200 mg/m^2	Day 2 to Day 4 (first dose on Day 2 is recommended to be administered in the afternoon)
SHP674#	IV (90±30 minutes)	BSA ≥0.6 m^2: 2500 IU/m^2 BSA <0.6 m^2: 82.5 IU/kg	Day 7
TIT: MTX, Ara-C, PSL#	IT	See Table 7.2.2.2.1-1	Day 1

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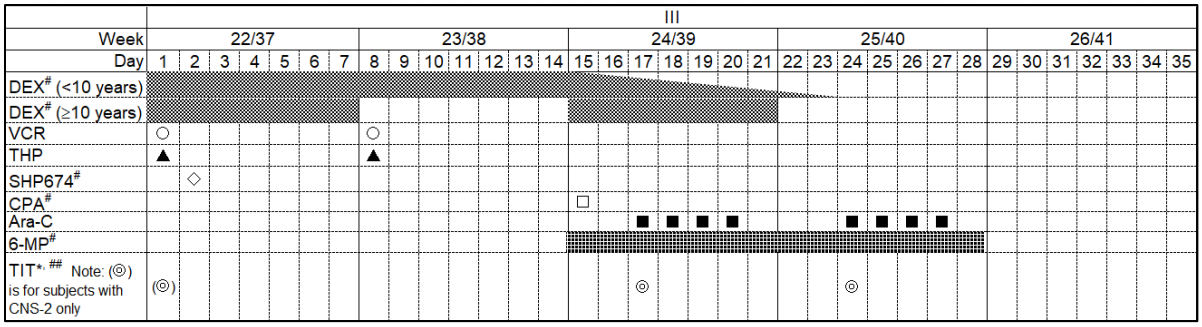
7.2.2.5 Re-induction Therapy (III/III+L)

7.2.2.5.1 III

The start day of the administration of DEX, VCR, or THP, whichever is administered first, will be regarded as Day 1. III is re-induction therapy for SR and IR. Treatment with DEX will be started on Day 1. The criteria for starting treatment with DEX must be followed not only before the start of III, but also on Day 15 of III (see Section 7.3.5). For subjects <10 years, DEX will be administered orally (or intravenously) at 10 mg/m^2/day divided into 3 doses per day from Day 1 to Day 14. Subsequently, the dose of DEX will be decreased to 5 mg/m^2 per day from Day 15 to Day 17, 2.5 mg/m^2 per day from Day 18 to Day 20, and 1.25 mg/m^2 per day from Day 21 to Day 23 (administration will be completed on Day 23). For subjects ≥10 years, DEX will be administered orally (or intravenously) at 10 mg/m^2/day from Day 1 to Day 7 and from Day 15 to Day 21. VCR will be administered intravenously at 1.5 mg/m^2 (maximum 2 mg) on Days 1 and 8. Pirarubicin hydrochloride (THP) will be administered intravenously for 60±15 minutes at 25 mg/m^2 on Days 1 and 8. CPA will be administered intravenously at 500 mg/m^2 for 60±15 minutes on Day 15. Ara-C will be administered intravenously by rapid injection or for ≤15 minutes once daily at 75 mg/m^2 from Day 17 to Day 20 and from Day 24 to Day 27. 6-MP will be administered orally at 60 mg/m^2 at bedtime from Day 15 to Day 28. The criteria for changes in treatment must be followed when starting treatment with Ara-C (see Section 7.4.5). In addition, MTX, Ara-C, and PSL will be administered intrathecally on Days 17 and 24 (TIT). Subjects with CNS-2 will receive an additional dose of TIT on Day 1. The doses of the intrathecal drugs are determined according to Table 7.2.2.1-1. TIT is allowed to be performed within 3 days of the prescribed day if there is a social reason such as that the prescribed day falls on a weekend or holiday. SHP674 will be administered intravenously for 90±30 minutes at 2500 IU/m^2 (if body surface area is ≥0.6 m^2) or at 82.5 IU/kg (if body surface area is <0.6 m^2) on Day 2. Points to note and criteria for changes in treatment must be followed during re-induction therapy (see Section 7.4.5).

Table 7.2.2.5.1-1 Dosing Schedule for III



* TIT is allowed to be performed within 3 days of the prescribed day if there is a social reason such as that the prescribed day falls on a weekend or holiday.
# To be provided by the Sponsor as an investigational product.
Only PSL will be provided by the Sponsor as an investigational product.

Table 7.2.2.5.1-2 Route of Administration, Dose, and Days of Administration of Drugs Used in III

Dose	Route of Administration	Dose	Days of Administration
DEX# for subjects <10 years	PO or IV in 3 doses	10 mg/m^2	Day 1 to Day 14
DEX# for subjects <10 years	PO or IV in 3 doses	5→2.5→1.25 mg/m^2	Day 15 to Day 23 (dose tapered for 9 days)
DEX# for subjects ≥10 years	PO or IV in 3 doses	10 mg/m^2	Day 1 to Day 7, Day 15 to Day 21
VCR	IV	1.5 mg/m^2 (up to 2 mg)	Day 1 and 8
THP	IV (60±15 minutes)	25 mg/m^2	Day 1 and 8
SHP674#	IV (90±30 minutes)	BSA ≥0.6 m^2: 2500 IU/m^2 BSA <0.6 m^2: 82.5 IU/kg	Day 2
CPA#	IV (60±15 minutes)	500 mg/m^2	Day 15
Ara-C	IV (by rapid injection or for ≤15 minutes)	75 mg/m^2	Day 17 to Day 20, Day 24 to Day 27
6-MP#	PO in one dose at bedtime	60 mg/m^2 (The dose will be adjusted according to the results of NUDT15 codon 139 polymorphism analysis. See Section 7.2.3-(7).)	Day 15 to Day 28
TIT*: MTX, Ara-C, PSL#	IT	See Table 7.2.2.2.1-1	Days 17 and 24; subjects with CNS-2 will receive an additional dose on Day 1.

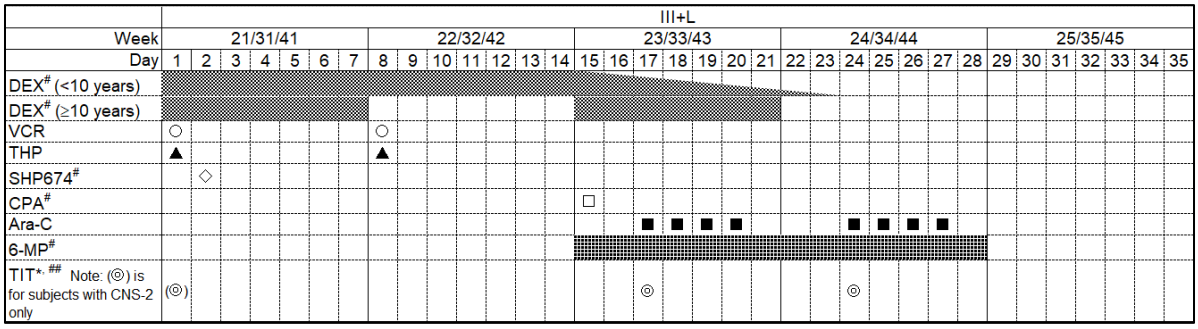
* TIT is allowed to be performed within 3 days of the prescribed day if there is a social reason such as that the prescribed day falls on a weekend or holiday.
# To be provided by the Sponsor as an investigational product.

7.2.2.5.2 III+L

The start day of the administration of DEX, VCR, or THP, whichever is administered first, will be regarded as Day 1. III+L is re-induction therapy for HR. Note that criteria for starting treatment must be followed not only before the start of III+L, but also on Day 15 of III+L (see Section 7.3.5). Treatment with DEX will be started on Day 1. For subjects <10 years, DEX will be administered orally (or intravenously) at 10 mg/m^2/day divided into 3 doses per day from Day 1 to Day 14. Subsequently, the dose of DEX will be decreased to 5 mg/m^2 per day from Day 15 to Day 17, 2.5 mg/m^2 per day from Day 18 to Day 20, and

1.25 mg/m^2 per day from Day 21 to Day 23 (administration will be completed on Day 23).The dose of DEX will be decreased by half every 3 days from Day 15 and decreased to 1.25 mg/m^2/day on Day 21. Treatment with DEX will be completed on Day 23. For subjects ≥10 years, DEX will be administered orally (or intravenously) at 10 mg/m^2/day from Day 1 to Day 7 and from Day 15 to Day 21. VCR will be administered intravenously at 1.5 mg/m^2 (maximum 2 mg) on Days 1 and 8. Pirarubicin hydrochloride (THP) will be administered intravenously for 60±15 minutes at 25 mg/m^2 on Days 1 and 8. CPA will be administered intravenously at 500 mg/m^2 for 60±15 minutes on Day 15. Ara-C will be administered intravenously by rapid injection or for ≤15 minutes once daily at 75 mg/m^2 from Day 17 to Day 20 and from Day 24 to Day 27. 6-MP will be administered orally at 60 mg/m^2 at bedtime from Day 15 to Day 28. The criteria for changes in treatment must be followed when starting treatment with Ara-C (see Section 7.4.5). In addition, MTX, Ara-C, and PSL will be administered intrathecally on Days 17 and 24 (TIT). Subjects with CNS-2 status will receive an additional dose of TIT on Day 1). The doses of the intrathecal drugs are determined according to Table 7.2.2.2.1-1. TIT is allowed to be performed within 3 days of the prescribed day if there is a social reason such as that the prescribed day falls on a weekend or holiday. SHP674 will be administered intravenously for 90±30 minutes at 2500 IU/m^2 (if body surface area is ≥0.6 m^2) or at 82.5 IU/kg (if body surface area is <0.6 m^2) on Day 2. Points to note and criteria for changes in treatment must be followed during re-induction therapy (see Section 7.4.5).

Table 7.2.2.5.2-1 Dosing Schedule for III+L



* TIT is allowed to be performed within 3 days of the prescribed day if there is a social reason such as that the prescribed day falls on a weekend or holiday.

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Only PSL will be provided by the Sponsor as an investigational product.

Table 7.2.2.5.2-2 Route of Administration, Dose, and Days of Administration of Drugs Used in III+L

Drug	Route of Administration	Dose	Days of Administration
DEX# for subjects <10 years	PO or IV in 3 doses	10 mg/m^2	Day 1 to Day 14
DEX# for subjects <10 years	PO or IV in 3 doses	5→2.5→1.25 mg/m^2	Day 15 to Day 23 (dose tapering for 9 days)
DEX# for subjects ≥10 years	PO or IV in 3 doses	10 mg/m^2	Day 1 to Day 7, Day 15 to Day 21
VCR	IV	1.5 mg/m^2 (up to 2.0 mg)	Days 1 and 8
THP	IV (60±15 minutes)	25 mg/m^2	Days 1 and 8
SHP674#	IV (90±30 minutes)	BSA ≥0.6 m^2: 2500 IU/m^2 BSA <0.6 m^2: 82.5 IU/kg	Day 2
CPA#	IV (60±15 minutes)	500 mg/m^2	Day 15
Ara-C	IV (by rapid injection or for ≤15 minutes)	75 mg/m^2	Day 17 to Day 20, Day 24 to Day 27
6-MP#	PO in one dose at bedtime	60 mg/m^2 (The dose will be adjusted according to the results of NUDT15 codon 139 polymorphism analysis. See Section 7.2.3-(7).)	Day 15 to Day 28
TIT*: MTX, Ara-C, PSL#	IT	See Table 7.2.2.2.1-1	Subjects with CNS-2 will receive an additional dose on Day 1. Days 17 and 24

* TIT is allowed to be performed within 3 days of the prescribed day if there is a social reason such as that the prescribed day falls on a weekend or holiday.
# To be provided by the Sponsor as an investigational product.

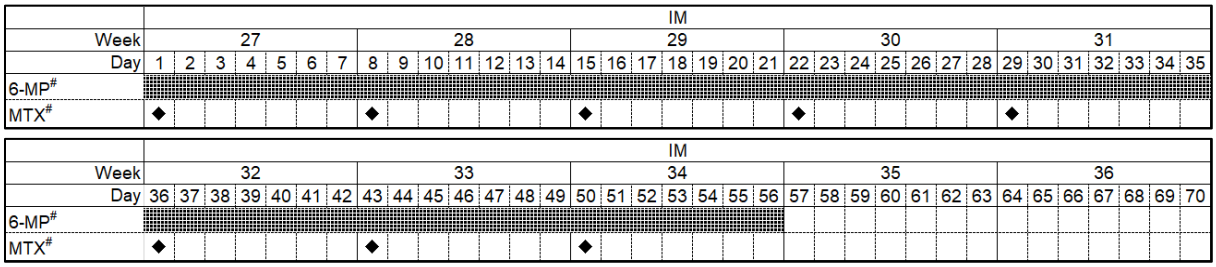
7.2.2.6 Interim Maintenance Therapy (IM)

A 10-week interim maintenance therapy (IM) will be performed in all of the subjects categorized as SR, IR, and HR, but the regimen will vary between the risk categories. IM will be performed once for 10 weeks in the SR and IR groups, whereas the 10-week IM will be divided in 2 periods (5 weeks × 2) in the HR group.

7.2.2.6.1 IM for SR

The start day of the administration of 6-MP or MTX, whichever is administered first, will be regarded as Day 1. MTX will be administered orally at 20 mg/m^2 on Days 1, 8, 15, 22, 29, 36, 43, and 50. 6-MP will be administered orally at 50 mg/m^2 once daily at bedtime from Day 1 to Day 56.

Table 7.2.2.6.1-1 Dosing Schedule for IM (SR)



To be provided by the Sponsor as an investigational product.

Table 7.2.2.6.1-2 Route of Administration, Dose, and Days of Administration of Drugs Used in IM for SR Subjects

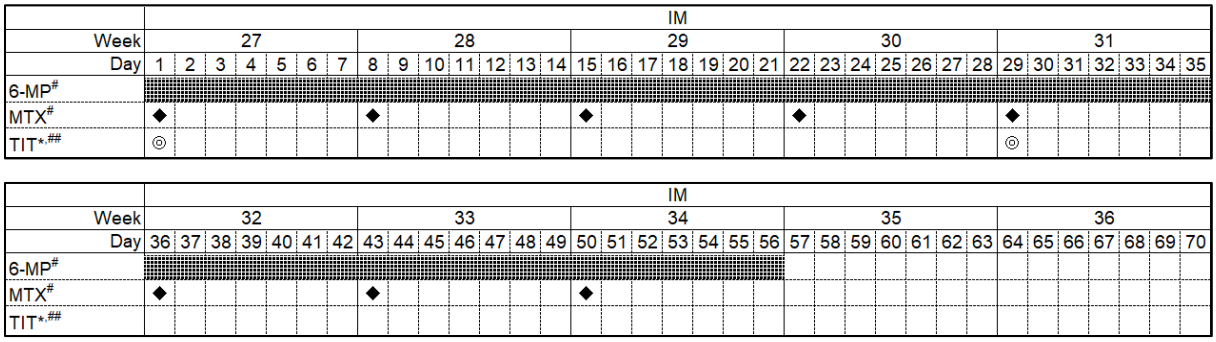
Drug	Route of Administration	Dose	Days of Administration
6-MP#	PO in one dose at bedtime	50 mg/m^2 (The dose will be adjusted according to the results of NUDT15 codon 139 polymorphism analysis. See Section 7.2.3-(7).)	Day 1 to Day 56
MTX#	PO in one dose	20 mg/m^2/week	Days 1, 8, 15, 22, 29, 36, 43, and 50

To be provided by the Sponsor as an investigational product.

7.2.2.6.2 IM for IR

The start day of the administration of 6-MP, MTX, or TIT, whichever is administered first, will be regarded as Day 1. MTX will be administered orally at 20 mg/m^2 on Days 1, 8, 15, 22, 29, 36, 43, and 50. 6-MP will be administered orally at 50 mg/m^2 once daily at bedtime from Day 1 to Day 56. In addition, MTX, Ara-C, and PSL will be administered intrathecally on Days 1 and 29 (TIT). The doses of the intrathecal drugs are determined according to Table 7.2.2.2.1-1. TIT is allowed to be performed within 3 days of the prescribed day if there is a social reason such as that the prescribed day falls on a weekend or holiday.

Table 7.2.2.6.2-1 Dosing Schedule for IM (IR)



* TIT is allowed to be performed within 3 days of the prescribed day if there is a social reason such as that the prescribed day falls on a weekend or holiday.
# To be provided by the Sponsor as an investigational product.
Only PSL will be provided by the Sponsor as an investigational product.

Table 7.2.2.6.2-2 Route of Administration, Dose, and Days of Administration of Drugs Used in IM for IR Subjects

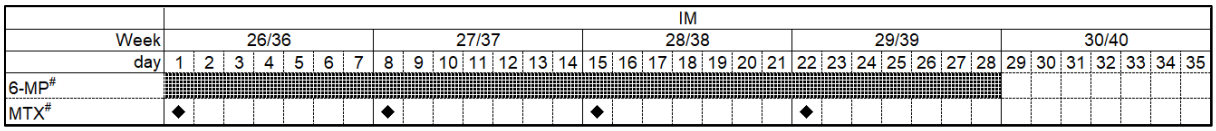
Drug	Route of Administration	Dose	Days of Administration
6-MP#	PO in one dose at bedtime	50 mg/m^2 (The dose will be adjusted according to the results of NUDT15 codon 139 polymorphism analysis. See Section 7.2.3-(7).)	Day 1 to Day 56
MTX#	PO in one dose	20 mg/m^2/week	Days 1, 8, 15, 22, 29, 36, 43, and 50
TIT*: MTX, Ara-C, PSL#	IT	See Table 7.2.2.2.1-1.	Days 1 and 29

* TIT is allowed to be performed within 3 days of the prescribed day if there is a social reason such as that the prescribed day falls on a weekend or holiday.
# To be provided by the Sponsor as an investigational product.

7.2.2.6.3 IM for HR

The start day of 6-MP or MTX administration will be regarded as Day 1. MTX will be administered orally at 20 mg/m^2 on Days 1, 8, 15, and 22. 6-MP will be administered orally at 50 mg/m^2 once daily at bedtime from Day 1 to Day 28.

Table 7.2.2.6.3-1 Dosing Schedule for IM (HR)



To be provided by the Sponsor as an investigational product.

Table 7.2.2.6.3-2 Route of Administration, Dose, and Days of Administration of Drugs Used in IM for HR Subjects

Drug	Route of Administration	Dose	Days of Administration
6-MP#	PO in one dose at bedtime	50 mg/m^2 (The dose will be adjusted according to the results of NUDT15 codon 139 polymorphism analysis. See Section 7.2.3-(7).)	Day 1 to Day 28
MTX#	PO in one dose	20 mg/m^2/week	Days 1, 8, 15, and 22

To be provided by the Sponsor as an investigational product.

7.2.3 Criteria for Changes in Treatment with Each Backbone Therapy Drug

If it is difficult to determine whether a subject should be withdrawn from the study, the investigator should consult with the Sponsor or the in-country caretaker. The definitions of terms used are provided below.

Dose reduction: To reduce the dose of a specific drug during treatment.

Specific-drug discontinuation: To stop administration of a specific drug or a treatment phase/block without resuming thereafter.

Interruption: To temporarily stop administration of a specific drug or the whole treatment phase/block in the course of treatment. Interruption is classified into the following categories 1) to 4):

1) Drug interruption: To temporarily stop administration of a part of the drugs included in a treatment phase/block, while the treatment phase/block itself is continued as prescribed (the administration of the interrupted drug will be resumed if required conditions are met). The term "drug interruption" is used for individual drugs.
2) Postponement: To postpone the prescribed start of the next whole treatment phase/block. The term "postponement" is used for individual treatment phases/blocks. As a result of postponement, the interval between treatment phases/blocks will be prolonged.
3) Treatment interruption: To temporarily stop administration of all drugs included in a treatment phase/block after the start of the treatment phase (the interrupted treatment will be resumed if required conditions are met).
4) Skip: To proceed to the next schedule without administering some or all of the drugs included in a treatment phase/block.

1) CPA

Criteria for Starting Second (Day 64) Treatment with CPA in Early Consolidation Therapy

Neutrophil count ≥500/μL and platelet count ≥50000/μL.

Skip and Dose Reduction

The administration of CPA will be skipped until Grade 3 or higher hemorrhagic cystitis symptoms accompanied by hematuria improve, resumed at half (1/2) of the original dose in the next phase if the hemorrhagic cystitis symptoms improve to Grade 1, and continued at the original dose (1/1) thereafter unless the symptoms worsen.

2) MTX

Dosing Criteria and Points to Note for HD-MTX Administration

Dosing Criteria for HD-MTX

The following criteria will be applied in addition to the criteria for starting treatment and the criteria for changes in treatment for each treatment phase:

1) Renal function: Serum creatinine does not exceed the age-specific ULN.
2) Liver function: D-Bil <1.5 mg/dL. For the second and subsequent doses, if AST or ALT is elevated after the previous administration, the subject must be judged by the investigator or subinvestigator that he or she can receive treatment.
3) There is no fluid retention such as pleural effusion and ascites, as judged by the investigator or subinvestigator based on clinical symptoms, test results, and other information.

Points to Note for HD-MTX Administration

1) Blood MTX concentrations will be measured at 24, 42, 48, and 66 hours post-dose. Additional measurement may be performed at other time points if the physician considers it necessary.
2) If any of the following symptoms is observed during the administration of HD-MTX, delayed excretion of MTX is suspected: acute diarrhea after the start of MTX administration, severe vomiting, and an evident increase in serum creatinine compared with the previous level. If severe hepatic disorder or acute renal failure (oliguric or nonoliguric) is noted in chemistry or blood coagulation test results, the administration of MTX will be skipped at the discretion of the investigator or

subinvestigator after recording the amount of MTX administered into the subject's body until that time.

3) Detailed procedure for LV rescue: If no abnormal blood MTX levels are observed, only 3 doses of 15 mg/m^2 LV will be administered 42, 48, and 54 hours after the start of MTX administration. At the investigative sites where the rapid measurement of the concentration at 54 hours is impossible, the administration of LV can be continued until the next blood MTX concentration obtained after the measurement at 48 hours becomes ≤0.25 μmoL/L (essential time point: 66 hours). Specifically, at such investigative sites, LV will be administered at the same dose 60 and 66 hours after the start of MTX administration subsequent to administration at 42, 48, and 54 hours. Whether the administration of LV can be stopped will be determined based on measurement at 66 hours. The details are presented in Table 7.2.3-1.
4) When administering HD-MTX, supportive care should be considered based on the following procedure used in the regimen of Study ALL-B12 and the "Precautions" section of the package insert for Methotrexate® Injection 1000 mg:
   a) Start fluid replacement at 3000 mL/m^2 per day not later than 3 hours before HD-MTX administration. Continue the fluid replacement until blood MTX concentration becomes ≤0.25 μmoL/L. If blood MTX concentration is above the upper limit of reference range, increase the amount of fluid replacement to 4500 mL/m^2 per day until the concentration decreases to the reference range. In this case, start fluid replacement at 4500 mL/m^2 per day at the next HD-MTX administration and thereafter.
   b) Maintain diuresis so that fluid balance is <+400 mL/m^2/12 hour. Administer 7 doses of acetazolamide (<5 years, 125 mg; ≥5 years, 250 mg) orally or intravenously every 6 hours from 12 hours before MTX administration. Fluid balance, urine pH, and other parameters should be assessed as appropriate to increase or decrease the dose of acetazolamide as needed.
   c) Mix 500 mL of maintenance fluid and 20 mL (16 to 20 mEq) of sodium bicarbonate (7% or 8.4%). Administer the solution until blood MTX concentration decreases to ≤0.25 μmoL/L. Make the best effort to keep urine pH at ≥7.0.

Table 7.2.3-1 Criteria for Blood MTX Concentrations and LV Rescue

Time of Blood MTX Concentration Measurement (hr)	MTX_{hr} Reference Value (μmol/L)	Rescue Time Point (hr)	Intravenous LV
24	TX_{hr} ≤150		
36	TX_{hr} ≤3.0		
42	TX_{hr} ≤1.0	42	15 mg/m^2
48	TX_{hr} ≤0.4	48	15 mg/m^2
54	TX_{hr} ≤0.25	54	15 mg/m^2
66	TX_{hr} ≤0.25		

Measures to Be Taken in Case of Abnormal Blood MTX Concentrations

- If the blood concentration at 24 hours is >150 μmoL/L, LV rescue (30 mg/m^2) will be started at 36 hours. In this case, the concentration at 42 hours should be obtained as soon as possible to immediately adjust the dose of LV since a further dose increase may be required.
- The rapid measurement at 36 hours (optional time point) is strongly recommended for subjects with a blood concentration of >150 μmoL/L at 24 hours, diuretic failure, or increased creatinine.

For other subjects, the blood concentration may be measured simultaneously with a sample at 42 hours after being collected as scheduled to check the data retrospectively (in this case, there will be no change in LV rescue for an abnormal level at 36 hours).

- If the blood concentration at 36 hours is >3 μmoL/L, LV rescue should be started immediately at 30 mg/m^2. In this case, the concentration at 42 hours should be obtained as soon as possible to immediately adjust the dose of LV since a further dose increase may be required.
- If the blood concentration at 42 hours is >1 μmoL/L but ≤5 μmoL/L, LV rescue will be continued according to Table 7.2.3-2 (even in this case, the blood concentration 66 hours after the start of MTX administration must be obtained to appropriately change the further schedule of LV administration). The dose of LV can be changed at the time when the blood concentration is determined (an additional dose may be administered before the next regular rescue time point).
- If the blood concentration at 42 hours is >5 μmoL/L, LV rescue will be continued according to the following formula until the concentration decreases to ≤5 μmoL/L. The dose of LV will be calculated based on the latest measurement: LV dose (mg) = MTX (μmoL/L) × weight (kg) (dose per 6 hours).
- If the blood concentration at 48 hours is >0.4 μmoL/L but ≤1 μmoL/L, it is not necessary to increase the dose of LV. The duration of treatment continuation will be determined based on the subsequent measurements. The action to be taken in the case of a blood concentration of >1 μmoL/L will be the same as at 42 hours.
- LV administration can be stopped at 3 doses without measurement at 54 hours only if a blood concentration of ≤0.25 μmoL/L is achieved at 48 hours. Even in this case, it is essential to measure the concentration at 66 hours. If the concentration again exceeds 0.25 μmoL/L, LV rescue should be re-started (15 mg/m^2).
- If the blood concentration at 54 hours is confirmed to be ≤0.25 μmoL/L, LV rescue will be stopped at 3 doses. If this criterion is not met (and ≤1.0 μmoL/L), LV will be administered at 15 mg/m^2 every 6 hours until the blood concentration decreases to ≤0.25 μmoL/L. The action to be taken in the case of a blood concentration of >1.0 μmoL/L will be the same as at 42 hours.
- For the investigative sites where the rapid measurement at 54 hours is impossible, LV will be administered at 60 and 66 hours additionally. LV rescue will be stopped if the blood concentration at 66 hours (essential time point) is ≤0.25 μmoL/L. If the blood concentration is >0.25 μmoL/L, LV will be administered at 15 mg/m^2 every 6 hours until the concentration becomes ≤0.25 μmoL/L.

For details, see **Dosing Criteria and Points to Note for HD-MTX Administration.**

Table 7.2.3-2 Blood MTX Concentrations at 42 Hours, 48 Hours, and Subsequent Time Points and Dose of LV

MTX (μmol/L)	0.25< C ≤1.0	1.0< C ≤2.0	2.0< C ≤3.0	3.0< C ≤4.0	4.0< C ≤5.0	5.0< C
LV (mg/m^2)	15	30	45	60	75	See below[a]
Route of administration	IV	IV	IV	IV	IV	IV[a]
Dosing interval	Every 6 hours	Every 6 hours	Every 6 hours	Every 6 hours	Every 6 hours	Every 6 hours

a: Dose of LV (mg) = MTX (μmoL/L) × MTX (μmoL/L) × body weight (kg).

Specific-drug discontinuation and Skip

Further treatment with MTX will be discontinued if a subject has leukoencephalopathy accompanied by neurologic symptoms or if any findings associated with Grade 3 or higher (CTCAE ver 5.0) leukoencephalopathy are noted on images. For further information, see **Dosing Criteria and Points to Note for HD-MTX administration**.

3) Ara-C

Criteria for Starting Treatment Phase for 4-Day Repeated Administration of Ara-C (Ara-C Treatment Phase) in Early Consolidation Therapy and Points to Note

1) Each Ara-C treatment phase should be started when white blood cell count is ≥500/μL.
2) Ara-C treatment phase should not be interrupted as far as possible (however, the treatment phase should be interrupted if neutrophil count is 0/μL).
3) If it is necessary to interrupt the Ara-C treatment phase, the administration of all other drugs that are included in Section 7 (Treatment Plan and Concomitant Treatments) should also be interrupted.

Specific-drug discontinuation

Ara-C will be discontinued if any of the following symptoms are noted:

Serious Ara-C syndrome: Symptoms such as high fever, skin erythema, and joint pain that are difficult to treat or prevent.

Grade 3 or higher CNS symptoms: Convulsion, serious consciousness disorder (coma, in particular), etc.

4) VCR

Skip and Dose Reduction

The administration of VCR will be skipped until Grade 3 or higher peripheral motor or sensory neuropathy improves, resumed at half of the original dose if the peripheral motor or sensory neuropathy improves to Grade 1, and continued at the same dose thereafter unless the symptom worsens. The dose of VCR will be reduced to half of the original dose when D-Bil is ≥1.5 mg/dL. The administration of VCR will be skipped when D-Bil is ≥2 mg/dL.

5) DEX

Determination of Treatment Strategy According to the Subject's Symptoms

Steroids will not be reduced or discontinued even if osteonecrosis is diagnosed, regardless of whether it is asymptomatic or symptomatic.

Switch to Injection

As with oral DEX, injectable DEX will be administered divided into 3 doses per day.

6) PSL

Determination of Treatment Strategy According to the Subject's Symptoms

1) Steroids will not be reduced or discontinued even if osteonecrosis is diagnosed, regardless of whether it is asymptomatic or symptomatic.
2) PSL will not be discontinued in TIT for subjects who are diagnosed with osteonecrosis, regardless of whether it is asymptomatic or symptomatic.

Switch to Injection

As with oral DEX, injectable DEX will be administered divided into 3 doses per day.

7) 6-MP

Determination of Treatment Strategy According to the Results of NUDT15 Codon 139 Polymorphism Analysis and the Subject's Symptoms

Arg/Arg type:

Treatment with 6-MP will be started at a usual dose. The dose of 6-MP will not be adjusted unless the criteria for dose changes specified in other sections (Sections 7.2.4 and 7.4.6) of the protocol are met.

Cys/Cys type:

As a general rule, treatment with 6-MP will be started at 1/10 of the usual dose. If it is difficult to continue treatment at 1/10 of the usual dose because of a TEAE that is related to 6-MP, the dose should be decreased appropriately at the discretion of the investigator or subinvestigator. If no TEAEs or other safety concerns related to 6-MP are observed at 1/10 of the usual dose or the observed TEAE or other safety concerns related to 6-MP are mild and if the investigator or subinvestigator determines that dose increase for the subject is possible, the dose of 6-MP can be increased to levels not exceeding the usual dose. This will not apply if the dose is adjusted according to Section 7.4.6.

Homozygous genotype other than Arg/Arg and Cys/Cys or heterozygous genotype:

As a general rule, treatment with 6-MP will be started at the usual dose. If it is difficult to continue treatment at the usual dose because of a TEAE related to 6-MP, the dose should be decreased appropriately at the discretion of the investigator or subinvestigator. If the TEAE related to 6-MP is relieved after dose reduction and if the investigator or subinvestigator determines that dose increase for the subject is possible, the dose of 6-MP can be increased to levels not exceeding the usual dose. This will not apply if the dose is adjusted according to Section 7.4.6.

7.2.4 Criteria for Changes in Treatment by Symptom

1) Renal toxicity

Treatment will be interrupted if Grade 4 renal dysfunction is observed during the treatment. The treatment will be resumed when the symptom is improved to Grade 2 or lower. The criteria for starting treatment with HD-MTX are specified separately. (See **Dosing Criteria and Points to Note for HD-MTX Administration**).

2) Cardiotoxicity

If left ventricular fractional shortening (FS) is <0.28 (corresponding to an ejection fraction [EF] of 0.63) on ultrasonography, the administration of DNR, THP, and CPA will be skipped until FS increases to ≥0.28.

3) Hepatotoxicity

If AST or ALT increases to ≥20-fold the age-specific ULN (Grade 4) during treatment, the treatment will be temporarily interrupted, and the administration of a liver protection drug will be started. If D-Bil is ≥1.5 mg/dL, treatment will be interrupted. As a general rule, treatment will be resumed when increased AST or ALT is improved to Grade 2 or lower (≤5-fold the age-specific reference level) and D-Bil decreases to <1.5 mg/dL. However, for AST and ALT levels, treatment can be resumed when the increased level decreases to ≤10-fold the age-specific ULN. In the treatment phases/blocks in which 6-MP is likely to be associated with hepatic dysfunction, 6-MP can be administered at half of the prescribed dose until AST or ALT decreases to ≤10-fold the age-specific ULN.

4) Hyperglycemia
   - Sustained fasting blood glucose level ≥250 mg/dL and negative (−) urinary ketones: Steroids will be administered at half of the prescribed dose.
   - Sustained fasting blood glucose level ≥250 mg/dL and positive (+) urinary ketones: Steroids will be interrupted. After improvement of blood glucose levels and ketoacidosis, the administration of steroids will be resumed at half of the prescribed dose.
5) Hypertriglyceridemia
   - Any increase in blood triglyceride levels will be managed by the investigator or subinvestigator according to their clinical judgment and established medical/institutional guidelines. In case of severe asymptomatic hypertriglyceridemia (i.e., TG levels of >1000 mg/dL and no association with acute pancreatitis), as first line therapy, dietary intervention followed by fibrates or other treatment of investigator's or subinvestigator's choice, including plasmapheresis, may be considered .
   - Administration of SHP674 will be left to the discretion of the investigator or subinvestigator. For SHP674 administration in early consolidation therapy (I_B+L) for HR, see item 2) of Section 7.4.3.

7.2.5 Prohibited Concomitant Therapies

7.2.5.1 Prohibited Concomitant Therapies throughout the Study

Any of the following therapies must not be conducted during the study as long as no relapse occurs:

1) Treatment with anticancer agents and anticancer therapies (e.g., chemotherapy, hormone therapy, immunotherapy, radiation therapy, exchange transfusion, leukapheresis) that are not prescribed in the protocol.
2) Systemic corticosteroid therapy for the treatment of cancer that is not prescribed in the protocol.
3) Hematopoietic stem cell transplantation
4) Treatment with pegylated preparations
5) Treatment with live vaccines (until 3 months after the end of treatment in Study SHP674-201).

7.2.5.2 Temporarily Prohibited Concomitant Therapies

As a general rule, trimethoprim-sulfamethoxazole combination should be stopped from 6 days before the start of HD-MTX administration.

As a general rule, trimethoprim-sulfamethoxazole combination and nonsteroidal antiinflammatory drugs should not be administered during the administration of MTX and until blood MTX concentration decreases to ≤0.25 μmol/L, since these drugs may cause delayed excretion of MTX.

7.2.6 Restricted Concomitant Medications

Concomitant medications that are not prescribed in the protocol should be used taking account of drug-drug interactions based on the Investigator's Brochure for SHP674 (see Sections 6.4 and 6.6), package insert for each medication, and institutional standards. The following is an example:

The use of antibiotics for infections should be avoided as far as possible during the administration of MTX or until blood MTX concentration decreases to ≤0.25 μmol/L, since the antibiotics may cause delayed excretion of MTX. The use of drugs that lead to acidic urine pH (furosemide, ethacrynic acid, thiazide diuretics) should also be avoided.

Note that a decrease in serum protein levels due to SHP674 may increase the toxicity of protein-binding drugs. It should also be noted that SHP674 may prevent metabolism and clearance of concomitant medications because of its actions on protein synthesis and liver function, or when coadministered with other chemotherapeutic agents that are known to interact with CYP enzymes.

7.3 Criteria for Starting Administration in Each Treatment Phase

Subjects will be assessed for the starting criteria before the start of treatment in each phase and on Day 15 of re-induction therapy (III, III+L).

The starting criteria for each treatment phase are described below.

7.3.1 Criteria for Starting Pre-treatment Phase (I_P)

Subjects enrolled will start fluid therapy. After adequate diuresis (recommendation: ≥50 mL/m^2/hour) is obtained, as judged by the investigator or subinvestigator, subjects will start treatment in the pre-treatment phase.

7.3.2 Criteria for Starting Remission Induction Therapy (I_A2/I_A4)

Subjects must meet all of the following criteria 1) to 3):

1) On or after Day 8 of study treatment.
2) No serious infections, concurrent diseases, or adverse events. Exceptionally, subjects can receive treatment if the concurrent disease is attributable to leukemia and expected to be relieved with anticancer agents.
3) If a subject has a severe infectious complication, or if treatment with anticancer agents is considered inappropriate for a subject, the administration of VCR, DNR, SHP674, and triple intrathecal therapy (TIT) (for subjects with CNS-2 status) can be postponed by up to 14 consecutive days during the treatment phase. However, the administration of PSL in the pre-treatment phase will be continued during the postponed period.

7.3.3 Criteria for Starting Early Consolidation Therapy (I_B/I_B+L)

Subjects must meet all of the following criteria 1) to 3):

1) On or after Day 36 of study treatment.
2) Neutrophil count ≥500/μL and platelet count ≥50000/μL. These laboratory values must be obtained at least 48 hours after the last dose of G-CSF and at least 3 days after the last platelet transfusion. However, subjects who do not meet the above criteria for 7 days after the end of administration of the last drug in remission induction therapy (I_A2/I_A4) will undergo a bone marrow examination (BMA3 must be conducted at least once within 7 days after the end of administration on Day 33, before the

start of early consolidation therapy [I_B/I_B+L]). Subjects with ≥5% blasts will start early consolidation therapy once white blood cell count increases to ≥1000/μL. Subjects with <5% blasts will start early consolidation therapy once neutrophil count increases to ≥500/μL and platelet count increases to ≥50000/μL. If it is difficult to determine whether the subject can start the next therapy 7 days after the end of administration on Day 33 (for example, the presence of blasts is suspected but not evident because of hypocellular bone marrow), an additional bone marrow examination will be performed at the time when white blood cell count increases to around 1000/μL to immediately start early consolidation therapy.

3) No serious infections, concurrent diseases, or adverse events.

7.3.4 Criteria for Starting Consolidation Therapy (M2/M5/HR3→HR2→HR1)

7.3.4.1 Criteria for Starting M2 and M5

Subjects must meet all of the following criteria 1) to 5):

1) Neutrophil count ≥500/μL and platelet count ≥50000/μL. These laboratory values must be obtained at least 48 hours after the last administration of G-CSF and at least 3 days after the last platelet transfusion. Subjects must meet this criterion also before the start of each HD-MTX administration.
2) No serious infections, concurrent diseases, or adverse events.
3) Renal function: Serum creatinine not exceeding the age-specific ULN.
4) Liver function: D-Bil <1.5 mg/dL and AST or ALT ≤5 × age-specific ULN. For the second and subsequent doses, if AST or ALT is elevated after the previous administration, the subject can receive treatment only when the investigator or subinvestigator judges that AST or ALT tends to decrease and the subject has no problems receiving treatment.
5) No fluid retention, including pleural effusion and ascites, as judged by the investigator or subinvestigator based on clinical symptoms, test results, and other information.

7.3.4.2 Criteria for Starting HR3, HR2, and HR1

Subjects must meet both of the following criteria 1) and 2):

1) Neutrophil count ≥500/μL and platelet count ≥50000/μL. These laboratory values must be obtained at least 48 hours after the last dose of G-CSF and at least 3 days after the last platelet transfusion.
2) No serious infections, concurrent diseases, or adverse events.

7.3.5 Criteria for Starting Re-induction Therapy (III/III+L)

Subjects must meet all of the following criteria 1) to 3). Subjects are required to meet criteria 1) and 2) when they start treatment from Day 15 onwards. However, even if a subject does not meet criteria 1) or 2) to start treatment from Day 15 onwards, DEX administration from Day 15 will be conducted as scheduled, whereas the administration of drugs other than DEX will be started after confirming that the subject meets the criteria for starting treatment.

1) Neutrophil count ≥500/μL and platelet count ≥50000/μL. These laboratory values must be obtained at least 48 hours after the last dose of G-CSF and at least 3 days after the last platelet transfusion.
2) No serious infections, concurrent diseases, or adverse events.
3) Subject has completed the washout period after the last dose in the preceding treatment phase (for 2 weeks after HD-MTX [M2/M5] and for 2 weeks for SR and IR and 1 weeks for HR after interim

maintenance therapy). If 6-MP is interrupted for myelosuppression or other reasons during treatment with HD-MTX and 6-MP alone is administered additionally after MTX, the washout period will be "2 weeks after the last dose of HD-MTX and 1 week after the last dose of 6-MP."

7.3.6 Interim Maintenance Therapy (IM)

Subjects must meet both of the following criteria 1) and 2):

1) Neutrophil count ≥500/μL and platelet count ≥50000/μL. These laboratory values must be obtained at least 48 hours after the last dose of G-CSF and at least 3 days after the last platelet transfusion.
2) No serious infections, concurrent diseases, or adverse events.

7.4 Points to Note and Criteria for Changes in Treatment in Each Phase

7.4.1 Points to Note and Criteria for Changes in Treatment during the Pre-treatment Phase (I_P)

1) For subjects having a large tumor burden in the body due to significant organomegaly or other conditions, the initial dose of PSL will be 0.2 to 0.5 mg/kg/day. The dose should be increased under monitoring of the subjects' symptoms, since these subjects frequently experience tumor lysis syndrome. Even in that case, the dose should be increased so that the total dosage from Day 1 to Day 7 will be ≥210 mg/m². If a total dosage of ≥210 mg/m² cannot be secured for a subject, the subject will be withdrawn from the study (see Section 5.1.1).
2) In the pre-treatment phase, if a subject has a white blood cell count of ≥100000/μL from Day 4 to Day 7 and the circulating blast count increased ≥1.5-fold that on Day 1, requiring earlier start of remission induction therapy including the administration of VCR on Day 8, the subject will be withdrawn from the study (see Section 5.1.1).
3) Subjects who have CNS-3 status at the cerebrospinal fluid examination on Day 1 will be withdrawn from the study (see Section 5.1.1).
4) Circulating leukemic cell count (lymphoblast count) will be assessed on Day 8, and the subject's risk category will be changed according to the following rules (see Section 3.1.3.1).
    - PGRs will be moved to SR or IR.
        - White blood cell count <50000/μL at the initial visit and age 1 to ≤9 years → SR
        - White blood cell count <50000/μL at the initial visit and age ≥10 years → IR
        - White blood cell count ≥50000/μL at the initial visit (regardless of age) → IR
    - PPRs will be moved to HR.

7.4.2 Points to Note and Criteria for Changes in Treatment during Remission Induction Therapy (I_A2/I_A4)

7.4.2.1 Points to Note and Criteria for Changes in Treatment during I_A2 in All the Groups and I_A4 in the IR Group

1) Circulating leukemic cell count (lymphoblast count) will be assessed on Day 8 (see Section 3.1.3.1). PPRs will be moved to the HR group.
2) Bone marrow will be assessed on Day 15 (BMA2). If Day 15 falls on a national holiday or a weekend, BMA2 can be performed ±1 day of Day 15. If BMA2 is performed on Day 16, the administration of

VCR and DNR on Day 15 should also be shifted to Day 16. VCR and DNR should be administered after the completion of BMA2).

3) Subjects will be moved to the HR group upon detection of any of the following factors before the start of treatment on Day 22:
   - *KMT2A-AFF1 (MLL-AF4)* fusion gene abnormality
   - Hypodiploid (≤44 chromosomes)

4) A bone marrow examination (BMA3) will be performed within 7 days from Day 33.

7.4.2.2 Points to Note and Criteria for Changes in Treatment during I_A4 in the HR Group

A bone marrow examination (BMA3) will be performed within 7 days from Day 33.

7.4.3 Points to Note and Criteria for Changes in Treatment during Early Consolidation Therapy (I_B/I_B+L)

1) Treatment will be interrupted when neutrophil count is 0/μL and will be resumed when neutrophil count is ≥200/μL. Treatment will not be interrupted based on white blood cell count. Treatment will be discontinued if it is interrupted for ≥28 consecutive days.

2) In the case of elevated blood triglyceride levels, administration of SHP674 will be left to the discretion of the investigator or subinvestigator according to item 5) of Section 7.2.4. If SHP674 administration on Day 38 is postponed, it may still take place at any time by Day 59 of early consolidation therapy (I_B+L), provided blood triglyceride levels have sufficiently subsided, according to the determination by the investigator or subinvestigator that resuming SHP674 administration is safe. However, this does not apply to the case where the Ara-C treatment phase must be interrupted (see Section 7.2.2.3).

7.4.4 Points to Note and Criteria for Changes in Treatment during Consolidation Therapy (M2/M5)

1) If a subject does not meet starting criterion 1) for the second and subsequent administrations of HD-MTX (see **Dosing Criteria and Points to Note for HD-MTX Administration**), 6-MP will be interrupted, and the administration of 2 g/m^2 (M2) or 5 g/m^2 (M5) HD-MTX will be started when criterion 1) is fulfilled. If the subject meets starting criterion 1) for the next HD-MTX administration after receiving HD-MTX with interrupted 6-MP, the administration of 6-MP will be resumed at the time of starting the next administration of HD-MTX. If the subject does not meet criterion 1) again after receiving HD-MTX without 6-MP, the subsequent dose of HD-MTX will be decreased to 1 g/m^2 (M2) or 2 g/m^2 (M5). If the subject again experiences a similar adverse event, further treatment with HD-MTX will be discontinued. The remaining doses of 6-MP after the fourth administration of HD-MTX will be administered. The period of the additional administration of 6-MP after the end of treatment with HD-MTX will be a maximum of 2 weeks.

2) If a subject experiences extensive oral mucosal disorders (CTCAE ver 5.0 Grade 4) after the administration of HD-MTX, the subsequent dose of HD-MTX will be decreased to 1 g/m^2 (M2) or 2 g/m^2 (M5). If the subject again experiences a similar adverse event, HD-MTX will then be administered at 1 g/m^2 (M2) or 2 g/m^2 (M5) for 6 hours. If the subject still experiences a similar adverse event, further treatment with HD-MTX will be discontinued.

3) If a subject experiences complications such as severe and extensive skin rash, encephalopathy, or renal failure caused by HD-MTX, further treatment with HD-MTX will be discontinued.

7.4.5 Points to Note and Criteria for Changes in Treatment during Re-induction Therapy (III/III+L)

1) Ara-C treatment block will be started when white blood cell count is ≥500/μL.
2) Treatment should be interrupted when neutrophil count is 0/μL and should be resumed when neutrophil count is ≥200/μL. Treatment will not be interrupted based on white blood cell count.
3) Treatment will be discontinued if it is interrupted for ≥28 days.

7.4.6 Points to Note and Criteria for Changes in Treatment during Interim Maintenance Therapy (IM)

Treatment in interim maintenance therapy (IM) is allowed to be changed at the discretion of the investigator or subinvestigator according to the following criteria for changes in treatment. The results of NUDT15 codon 139 polymorphism analysis must be considered when determining the starting dose of 6-MP (see Section 7.2.3 7)).

1) Adjustment of Doses of MTX and 6-MP

The dose will be adjusted to maintain a peripheral white blood cell count of 2000 to 3000/μL and a peripheral lymphocyte count of ≥300/μL. The criteria for adjustment are as follows:

- Treatment will be initiated at the starting dose. The dose will be adjusted as below based on peripheral blood findings 2 weeks after the start of treatment.
- The dose will continue to be adjusted after the first remeasurement of peripheral counts. For this purpose, the peripheral counts will be remeasured as needed after the first remeasurement.
- White blood cell count ≥3000/μL: The dose of 6-MP will be increased by 25%, without changing the dose of MTX, and the white blood cell count will be remeasured 2 weeks after increasing the dose of 6-MP. If the white blood cell count is still ≥3000/μL, the dose of MTX will be increased by 25%, without changing the dose of 6-MP, and the white blood cell count will be remeasured 2 weeks after increasing the dose of MTX. If the white blood cell count still remains ≥3000/μL, the dose of 6-MP will be increased by 25%, and the white blood cell count will be remeasured 2 weeks after increasing the dose of 6-MP. However, if the absolute lymphocyte count is ≤300/μL, which increases the risk of infections, the dose reduction criteria based on lymphocyte counts must be prioritized even when the white blood cell count is ≥3000/μL.
- White blood cell count 2000 to <3000/μL: No dose change.
- White blood cell count 1500 to <2000/μL: The dose of 6-MP will be reduced by 25%, without changing the dose of MTX. The white blood cell count will be remeasured 2 weeks after reducing the dose of 6-MP.
- White blood cell count <1500/μL: Both 6-MP and MTX will be interrupted for 2 weeks. The white blood cell count will be remeasured after the 2-week dose interruption.
- Lymphocyte count <300/μL: The dose of 6-MP will be reduced by 50%, without changing the dose of MTX. The lymphocyte count will be remeasured 2 weeks after reducing the dose of 6-MP.

- If the white blood cell count or lymphocyte count does not improve at the remeasurement 2 weeks after dose increase or reduction, the dose may be adjusted at the discretion of the investigator or subinvestigator.

2) Adjustment in the Case of Dose Interruption during Interim Maintenance Therapy (IM)

If MTX or 6-MP is interrupted because of myelosuppression or any other adverse event and the treatment is resumed within 6 days of interruption, the duration of maintenance therapy will remain unchanged, without administering the scheduled doses that were not administered during interruption. If the drug is interrupted for 7 or more days, the duration of maintenance therapy will be extended on a weekly basis to administer the scheduled doses that were not administered during interruption.

7.5 Tolerability Assessment in Part 1

Tolerability assessment in Part 1 will be based on the number of subjects who experience intolerable toxicity during the 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). Any intolerable toxicity will be followed until Day 37* and will not be considered “intolerable” if the toxicity recovers to Grade 2 or lower. If the intolerable toxicity does not recover to Grade 2 or lower by Day 37*, treatment will be discontinued.

* Tolerability assessment should be continued until Day 37. If the assessment cannot be conducted on Day 37, it may take place within +1 day of Day 37 but before the administration of Ara-C (for HR, Ara-C and SHP674).

7.5.1 Tolerability Assessment Period

The tolerability assessment period is defined as the 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). If the tolerability assessment cannot be conducted on Day 37, it may take place within +1 day of Day 37 but before the administration of Ara-C (for HR, Ara-C and SHP674).

7.5.2 Definition of Intolerable Toxicity

Intolerable toxicity is defined as the following toxicity that is observed during the tolerability assessment period. A TEAE for which a causal relationship to SHP674 is evidently ruled out will not be considered toxicity.

Grade 3 or higher toxicity (that does not improve to Grade 2 or lower by Day 37), with the exception of adverse drug reactions stated in the package inserts for PSL, DNR, VCR, L-asparaginase, MTX, Ara-C, CPA, and 6-MP (examples are presented in 7.5.3 Expected Toxicity), will be considered intolerable. Any expected toxicity that is more severe than usual and judged by the physician to be intolerable will also be regarded as intolerable toxicity. An SHP674-related TEAE that leads to interruption of early consolidation therapy for ≥28 days will also be regarded as intolerable toxicity if confirmed by the internal safety committee (composed of the Sponsor and study investigators) taking into consideration the expectedness and severity of the event according to section 7.5.5. The investigator or subinvestigator will report the occurrence of intolerable toxicity to the Sponsor or the in-country caretaker in an Intolerable Toxicity Report form (Attachment 7 to the protocol [supplement]) immediately after the end of Day 37.

7.5.3 Expected Toxicity

SOC (Internationally Agreed Order)	Expected Toxicity
Infections and infestations	Viral infection, infection, bacterial infection, opportunistic infection, sepsis, pneumonia, cystitis
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Lymphoma, acute leukaemia, myelodysplastic syndrome, secondary malignancy
Blood and lymphatic system disorders	Lymphadenopathy, coagulopathy, hypercoagulation, blood disorder, haematotoxicity, thrombocytopenia, eosinophilia, bone marrow failure, aplastic anaemia, haemorrhagic diathesis, erythropenia, increased tendency to bruise, leukopenia, leukocytosis, pancytopenia, anaemia, agranulocytosis, granulocytopenia
Immune system disorder	Anaphylactic shock, anaphylactic reaction, hypersensitivity, hypogammaglobulinaemia, immunosuppression
Endocrine disorder	Cushingoid, inappropriate antidiuretic hormone secretion, hyperthyroidism, secondary adrenocortical insufficiency, adrenocortical insufficiency, endocrine pancreatic disorder
Metabolism and nutrition disorders	Hyperammonaemia, hyperkalaemia, hyperphosphataemia, hyperglycaemia, hyperlipidaemia, hyperuricaemia, tumour lysis syndrome, decreased appetite, increased appetite, polydipsia, glucose tolerance impaired, metabolic acidosis, hypokalaemia, alkalosis hypokalaemic, hypocalcaemia, hyponatraemia, blood hyposmosis, hypoproteinaemia, electrolyte imbalance, diabetes mellitus
Mental disorder	Depression, irritability, confusional state, disorientation, nervousness, mental disorder, mental status changes, euphoric mood, anxiety, insomnia, depressive symptom
Nervous system disorder	Depressed level of consciousness, loss of consciousness, altered state of consciousness, ataxia, posterior reversible encephalopathy syndrome, hypoaesthesia, nystagmus, hypotonia, somnolence, language disorder, epidural lipomatosis, hypertensive encephalopathy, coma, paraesthesia, autonomic neuropathy, myasthenia gravis, cerebellar ataxia, nervous system disorder, neuralgia, neurotoxicity, intracranial pressure increased, headache, widespread structural disorder of the brain, cerebral infarction, cerebral haemorrhage, encephalopathy, cranial nerve disorder, leukoencephalopathy, hyporeflexia, dizziness, balance disorder, paralysis, neuropathy peripheral, peripheral motor neuropathy, peripheral sensory neuropathy, dysgeusia, seizure, peroneal nerve palsy
Eye disorders	Blindness transient, exophthalmos, ocular hyperaemia, ocular hypertension, optic atrophy, dysmetropsia, visual acuity reduced, cataract subcapsular, diplopia, metamorphopsia, vision blurred, retinal disorder, retinal pigment epitheliopathy, retinal detachment, chorioretinopathy, glaucoma
Ear and labyrinth disorders	Vertigo, deafness
Cardiac disorders	Angina pectoris, cardiac tamponade, myocardial ischaemia, myocardial infarction, myocardial damage, cardiotoxicity, pericardial effusion, cardiac failure, pericarditis, palpitations, tachycardia
Angiopathy	Shock, orthostatic hypotension, vasculitis, angiopathy, vascular pain, thrombosis, thrombophlebitis, hypertension, haemorrhage, gastrointestinal haemorrhage, phlebitis, flushing, hypotension, aneurysm
Respiratory, thoracic and mediastinal disorders	Cough, interstitial lung disease, pneumomediastinum, acute respiratory distress syndrome, pleural effusion, dyspnoea, respiratory failure, oropharyngeal pain, pulmonary haemorrhage, pulmonary fibrosis, nasal discomfort, wheezing asthma

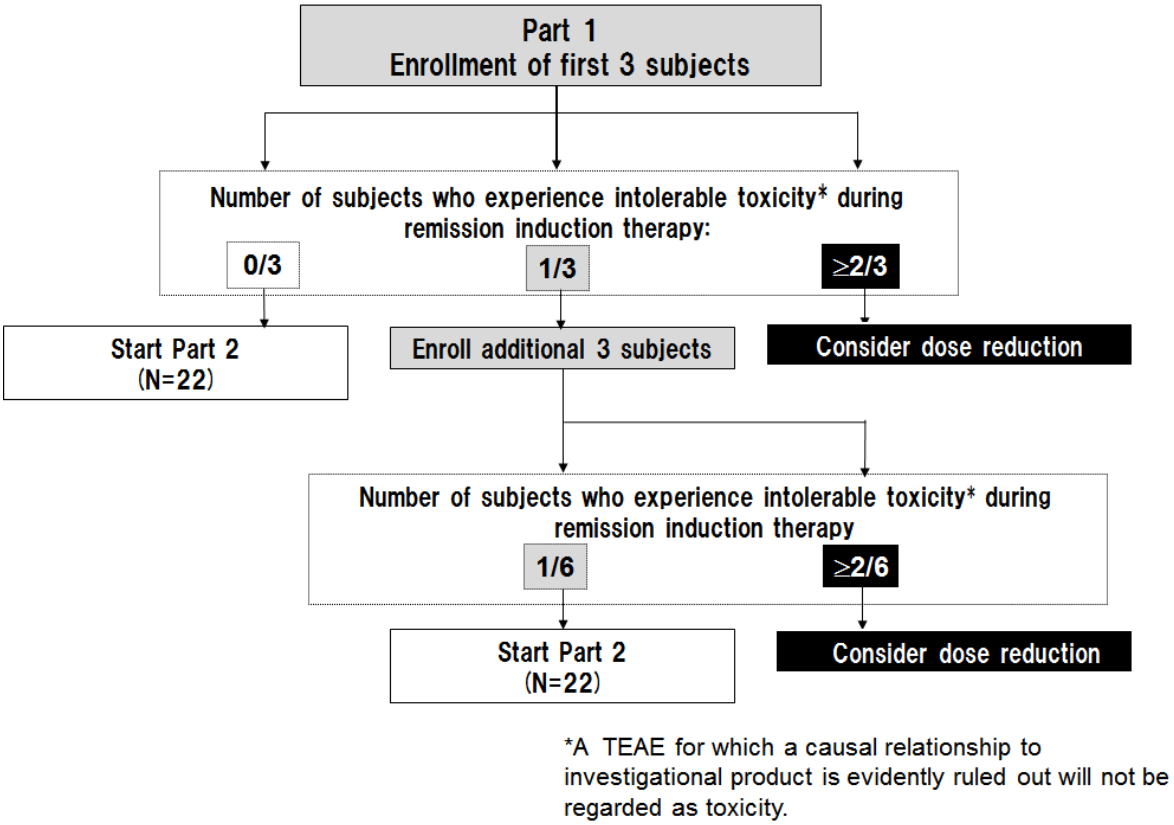
SOC (Internationally Agreed Order)	Expected Toxicity
Gastrointestinal disorder	Ileus, eructation, melaena, nausea, gastrointestinal disorder, gastrointestinal ulcer, diarrhoea, necrotising colitis, pancreatitis acute, mouth ulceration, lip swelling, stomatitis, neutropenic colitis, pancreatitis relapsing, enterocolitis haemorrhagic, gastrointestinal motility disorder, gastrointestinal disorder, gastrointestinal perforation, peptic ulcer, dyspepsia, abdominal pain upper, glossitis, enterocolitis, intestinal paralysis, pneumatosis intestinalis, abdominal pain, abdominal distension, constipation, ileus paralytic, vomiting, insulitis, pancreatitis
Hepatobiliary disorders	Jaundice, hepatic necrosis, hepatic function abnormal, hepatic cirrhosis, liver disorder, hepatic vein occlusion, hepatic fibrosis, hepatic failure, hepatitis fulminant, hepatic steatosis
Skin and subcutaneous tissue disorders	Acne, pruritus, nodular rash, angioedema, photosensitivity reaction, erythema, purpura, panniculitis, lipohypertrophy, pigmentation disorder, hyperhidrosis, hypertrichosis, alopecia, toxic epidermal necrolysis, naildeformity, nail discolouration, rash, ecchymosis, dermatitis, skin depigmentation, skin fragility, skin striae, skin ulcer, oculomucocutaneous syndrome, skin exfoliation, skin thinning, urticaria
Musculoskeletal and connective tissue disorders	Myopathy, rhabdomyolysis, arthralgia, muscle atrophy, muscle disorder, myalgia, muscle spasms, nuchal rigidity, osteonecrosis, osteoporosis, back pain, convulsion
Renal and urinary disorders	Nephrotic syndrome, acute kidney injury, scleroderma renal crisis, haematuria, azotaemia, hypersthenuria, cystitis haemorrhagic, renal impairment, nephropathy, renal disorder, renal tubular necrosis, renal failure, polyuria, protein urine, urinary retention, calculus urinary, dysuria, oliguria, bladder disorder
Reproductive system and breast disorders	Menstrual disorder, gonadopathy, amenorrhoea, azoospermia, ovarian failure
General disorders and administration site conditions	Influenza like illness, chills, chest discomfort, malaise, thirst, induration, impaired healing, injection site reaction, developmental delay, pyrexia, fatigue, discomfort, oedema, gait disturbance, asthenia, withdrawal syndrome, feeling cold, pain
Investigations	Gamma-glutamyltransferase increased, aspartate aminotransferase increased, amylase increased, alanine aminotransferase increased, antithrombin iii decreased, plasminogen decreased, protein c decreased, prothrombin level decreased, liver function test abnormal, intraocular pressure increased, megaloblasts increased, blood pressure increased, blood pressure decreased, platelet count decreased, blood alkaline phosphatase increased, blood albumin decreased, blood creatinine increased, blood creatine phosphokinase increased, blood cholinesterase decreased, blood sodium decreased, blood fibrinogen decreased, blood glucose increased, myoglobin blood increased, blood lactate dehydrogenase increased, blood uric acid increased, blood urea increased, eosinophil count increased, bone density decreased, ECG signs of myocardial ischaemia, electrocardiogram abnormal, spermatozoa progressive motility abnormal, sperm concentration abnormal, red blood cell count decreased, weight decreased, weight increased, nitrogen balance negative, urine sodium increased, myoglobin urine present, white blood cell count decreased, white blood cell count increased, reticulocyte count decreased, pancreatic enzymes increased
Injury, poisoning and procedural complications	Fat embolism, tendon rupture

7.5.4 Procedure for Tolerability Assessment

The Sponsor or in-country caretaker and the medical officer will assess tolerability in 3 subjects who receive SHP674. The second and third subjects will start the pre-treatment phase at least 72 hours after the preceding subject receives SHP674 on Day 12 of remission induction therapy. Tolerability issues will be considered not present if 0 of the 3 subjects experience intolerable toxicity (see Section 7.5.2). If 0 of 3 subjects experience intolerable toxicity tolerability issues will be considered not present, the dose will be confirmed and the study will move to Part 2. If 1 of the 3 subjects experiences intolerable toxicity, additional 3 subjects will be enrolled in the study. Tolerability issues will be considered not present if 1 of the 6 subjects experiences intolerable toxicity. If ≥2 of the 3 subjects or ≥2 of the 6 subjects experience intolerable toxicity, the Sponsor or in-country caretaker and the medical officer will discuss the necessity of dose reduction, and the Sponsor will make a final decision whether to reduce the dose of SHP674.

In the case that tolerability cannot be assessed adequately, for example, if a subject enrolled does not start treatment with SHP674 for any reason or if a subject is withdrawn from the study during the tolerability assessment period for a reason other than a tolerability issue, enrollment of an additional subject will be considered.

Figure 7.5.4-1 Outline of Tolerability Assessment Procedure



7.5.5 Decision on Whether to Move to Part 2

Safety data of Part 1 will be reviewed by an internal safety committee that will determine if the dose investigated in Part 1 was well tolerated and Part 2 can be initiated with this dose.

8 STUDY PROCEDURES AND SCHEDULE

The schedule for study procedures during the period from informed consent through remission induction therapy, which is common to SR, IR, and HR, is presented in Table 8-1. The schedule for early consolidation therapy and subsequent therapies is presented in Table 8-2 (SR and IR) and Table 8-3 (HR).

Table 8-1 Schedule for Study Procedures from Informed Consent through Remission Induction Therapy (Common to SR, IR, and HR)

				Ip	I_A2/I_A4												
	Informed Consent [g]	Screening [h]	Enrollment	Week 1	Week 2				Week 3		Week 4			Week 5			
Day [a]	-21	-14		1 [i]	8	12	13	14	15	16	22	23	26	29	30	33	37
Hospitalization [b]					←												→
Informed consent	X																
Inclusion and exclusion criteria		X															
Subject demographics		X															
Enrollment			X														
Criteria for starting treatment [c]				X	X												
Disease assessment and risk classification		X			X [k]				X [l]		X [n]					X [o]	
Symptoms and findings		X		X	X	X			X		X			X			
Height and weight [d],[f]		X		X	X												
Vital signs [d]		X		X	X	X			X		X			X			
ECOG PS [d],[e]		X		X	X	X			X		X			X			
SpO_2		X															
Hematology [d],[e]		X		X	X	X			X		X			X			
Chemistry [d],[e]		X		X	X	X			X		X			X			
Coagulation test [d],[e]		X		X	X	X			X		X			X			
Immunoserological test [d],[e]		X		X	X												
Viral test		X															
Urinalysis [d],[e]		X		X	X	X			X		X			X			
Echocardiography		X															
CT, MRI, PET		X														X [p]	
Pregnancy test		X															
12-lead resting electrocardiography		X			*See Table 8.15-1.												
Bone marrow examination									X [m] BMA2							X [q] BMA3	
Cerebrospinal fluid examination				X [j]												X [r]	
Blood MTX concentration																	
Plasma asparaginase activity					*See Table 8.22-1.												
Immunogenicity (anti-antibodies)					*See Table 8.22-2.												
Adverse events	←																→
Review of concomitant medications and therapies, supportive care	←																→
[redacted]																	

a) If treatment is postponed, the relevant test schedule will also be postponed.
b) As a general rule, subjects will be hospitalized during remission induction therapy.
c) Laboratory results obtained within 4 days before the start of treatment in each phase may be used to assess subjects for the criteria for starting treatment related to hematology or chemistry.
d) To be performed before the start of the administration of SHP674 or the backbone therapy drugs that are listed in Section 7.2.1 (7.2.1 Backbone Therapy Drugs Used in This Study).
e) The test or examination is allowed to be performed within 4 days before the prescribed day, except for that at screening and on I_P Day 1.
f) Height and weight are allowed to be measured within 7 days before the prescribed day, except for those at screening and on I_P Day 1.
g) Informed consent must be obtained not later than 21 days before enrollment.
h) Screening must be performed not later than 14 days before enrollment.
i) Treatment in the pre-treatment phase will be started within 7 days after enrollment. If screening is performed within 3 days before Day 1, the duplicate test items scheduled for Day 1 pre-dose may be omitted, except for symptoms and findings and vital signs,.
j) Cerebrospinal fluid examination will be performed simultaneously with MTX-IT on I_P Day 1. However, it can be postponed until up to Day 4, if a subject cannot receive MTX IT on Day 1 for a reason such as that the subject's initial visit falls on a weekend.
k) Oral administration (or IV administration at the same dose) of PSL will be started on I_P Day 1. A subject who has a circulating leukemic cell count (lymphoblast count) of <1000/μL on Day 8 is defined as a prednisolone good responder (PGR). A subject who has a circulating leukemic cell count (lymphoblast count) of ≥1000/μL on Day 8 is defined as a prednisolone poor responder (PPR). Circulating leukemic cell count will be calculated by multiplying circulating white blood cell count (/μL) measured on the same day by the percentage of leukemic cells (%). Results of smear microscopy at each investigative site will be used to determine the response to PSL. A total dosage of PSL of ≥210 mg/m^2 is required to determine the response to PSL. The test required for the determination of PSL response should be performed

before the start of administration of the investigational product or backbone therapy drugs listed in Section 7.2.1 (Backbone Therapy Drugs Used in This Study).

l) Risk category will be determined before administration on I_A2/I_A4 Day 22 based on the result of the bone marrow examination (BMA2) performed on I_A2/I_A4 Day 15.

m) On Day 15 of I_A2/I_A4, VCR and DNR should be administered after the completion of BMA2. If Day 15 of I_A2/I_A4 falls on a national holiday or a weekend, BMA2 can be performed ±1 day of Day 15. If BMA2 is performed on Day 16, the administration of VCR and DNR scheduled for Day 15 of I_A2/ I_A4 should also be shifted to Day 16.

n) Whether to categorize a subject as HR will be determined based on the results of chimeric gene analysis and chromosome analysis. The determination should be completed before the start of administration of the investigational product or backbone therapy drugs listed in Section 7.2.1 (Backbone Therapy Drugs Used in This Study).

o) Risk category will be determined based on the results of BMA3.

p) As a general rule, PET will be performed in the fasting state.

q) To be performed within 7 days after the end of administration on Day 33 of I_A2/I_A4.

r) To be performed from Day 33 of I_A2/I_A4 to before the start of early consolidation therapy (I_B/I_B+L). If the day of TIT is changed for a social reason such as that the prescribed day falls on a weekend or holiday, the day of bone marrow examination may also be changed accordingly.

[redacted]

Table 8-2 Schedule for Study Procedures in Early Consolidation Therapy and Subsequent Therapies (SR/IR)

	I_B						M2/M5																				
	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11	Week 12	Week 13				Week 14	Week 15				Week 16	Week 17				Week 18	Week 19				Week 20	Week 21
Day [a]	36	43	50	57	64	71	1	8	9	10	11	15	22	23	24	25	29	36	37	38	39	43	50	51	52	53	57 [m]	64 [m]
Criteria for starting treatment [b]	X				X		X	X					X					X					X					
Symptoms and findings [c]	X	X	X	X	X	X [e]	X	X				X	X				X	X				X	X				X	X
Height and weight [c],[d]	X						X																					
Vital signs [c]	X	X	X	X	X	X [e]	X	X				X	X				X	X				X	X				X	X
ECOG PS [c],[e]	X	X	X	X	X	X	X	X				X	X				X	X				X	X				X	X
SpO_2																												
Hematology [c],[e]	X	X	X	X	X	X	X	X				X	X				X	X				X	X				X	X
Chemistry [c],[e]	X	X	X	X	X	X	X	X				X	X				X	X				X	X				X	X
Coagulation test [c],[e]	X	X	X	X	X	X	X	X				X	X				X	X				X	X				X	X
Immunoserological test [c],[e]	X						X																					
Viral test [c],[e]	X [f]						X [f]																					
Urinalysis [c],[e]	X						X																					
Electrocariography																												
CT, MRI, PET						X [g]																						
Pregnancy test																												
12-lead resting electrocardiography [c],[e]	X						X																					
Bone marrow examination						X [h] BMA4																						
Cerebrospinal fluid examination						X [i]																						
Blood MTX concentration									X [j]	X [k]	X [l]			X [j]	X [k]	X [l]			X [j]	X [k]	X [l]			X [j]	X [k]	X [l]		
Plasma asparaginase activity	*See Table 8.22-1.																											
Immunogenicity (anti-antibodies)	*See Table 8.22-2.																											
Adverse events	←																											→
Review of concomitant medications and therapies, supportive care	←																											→
[redacted]																												

Table 8-2 Schedule for Study Procedures in Early Consolidation Therapy and Subsequent Therapies (SR/IR) (Continued)

	III									IM		III								
	Week 22		Week 23		Week 24		Week 25		Week 26	Week 27	Week 28 to Week 36	Week 37		Week 38		Week 39		Week 40		Week 41	Treatment completion/ discontinuation or study discontinuation [o]
Day [a]	1	2	8	13	15	16	22	27	29 [m]	1	8,15,22... 50,57 [m],64 [m]	1	2	8	13	15	16	22	27	29 [m]	
Criteria for starting treatment [b]	X				X					X		X				X					
Symptoms and findings [c]	X	X	X		X		X		X	X	X [n]	X	X	X		X		X		X	X [p]
Height and weight [c],[d]	X									X		X									X [p]
Vital signs [c]	X	X	X		X		X		X	X	X [n]	X	X	X		X		X		X	X [p]
ECOG PS [c],[e]	X	X	X		X		X		X	X	X	X	X	X		X		X		X	X [p]
SpO_2																					X [p]
Hematology [c],[e]	X	X	X		X		X		X	X	X	X	X	X		X		X		X	X [p]
Chemistry [c],[e]	X	X	X		X		X		X	X	X	X	X	X		X		X		X	X [p]
Coagulation test [c],[e]	X	X	X		X		X		X	X	X	X	X	X		X		X		X	X [p]
Immunoserological test [c],[e]	X									X		X									X [p]
Viral test [c],[e]	X [f]									X [f]		X [f]									X [f],[p]
Urinalysis [c],[e]	X	X								X		X	X								X [p]
Electrocariography																					X [p]
CT, MRI, PET																					
Pregnancy test																					X [p]
12-lead resting electrocardiography [c],[e]	X									X		X									X [p]
Bone marrow examination																					
Cerebrospinal fluid examination																					
Blood MTX concentration																					
Plasma asparaginase activity	*See Table 8.22-1.																				
Immunogenicity (anti-antibodies)	*See Table 8.22-2.																				
Adverse events	←																			→	
Review of concomitant medications and therapies, supportive care	←																			→	
[redacted]																					

a) If treatment is postponed, the relevant test schedule will also be postponed.
b) Laboratory results obtained within 4 days before the start of treatment in each phase may be used to assess subjects for the starting criteria related to hematology or chemistry.
c) To be performed before the start of the administration of SHP674 or the backbone therapy drugs that are listed in Section 7.2.1 (Backbone Therapy Drugs Used in This Study)
d) Height and weight are allowed to be measured within 7 days before the prescribed day, except for those at treatment completion, treatment discontinuation, or study discontinuation.
e) Laboratory tests are allowed to be performed within 4 days before the prescribed day, except for those at treatment completion, treatment discontinuation, or study discontinuation.
f) If the subject is negative for HBs antigen and positive for HBc antibody or HBs antibody at screening, HBV DNA will be measured to confirm that the result is negative. HBV DNA measurement other than that at screening will not be required for subjects with a documented history of HBV vaccination.
g) As a general rule, PET should be performed in the fasting state.
[redacted]
i) To be performed during the period from Day 59 of $I_{B/}$ I_B+L to before the start of consolidation therapy (M2/M5/HR3). If the day of TIT is changed for a social reason such as that the prescribed day falls on a weekend or holiday, the day of bone marrow examination may also be changed accordingly.
j) To be performed 24 hours after the administration of MTX.
k) To be performed 42 and 48 hours after the administration of MTX. Measurement at 36 hours is optional.
l) To be performed 66 hours after the administration of MTX. Measurement at 54 hours is optional.
m) Tests and assessments on M2/M5 Day 57, M2/M5 Day 64, III Day 29, IM Day 57, and IM Day 64 can be omitted if the investigator or subinvestigator considers unnecessary. If not omitted, these tests and assessments are allowed to be performed within 4 days before the prescribed day.
n) The assessment is allowed to be performed within 4 days before the prescribe day.
o) To be performed 30 (+7) days after the last dose of investigational product.
p) If the subject's next therapy starts 30 (+7) days after the last dose of investigational product or earlier, the assessment may be performed during the period from 7 days before the start date of the next therapy to before the start of the next therapy.

Table 8-3 Schedule for Study Procedures in Early Consolidation Therapy and Subsequent Therapies (HR)

	I_B+L							HR3				HR2						
	Week 6		Week 7	Week 8	Week 9	Week 10	Week 11	Week 12		Week 13	Week 14	Week 15				Week 16	Week 17	
Day [a]	36	38[g]	43	50	57	64	71	1	6	8[k]	15[k]	1	2	3	4	6	8[k]	15[k]
Criteria for starting treatment [b]	X					X		X				X						
Symptoms and findings [c]	X	X	X	X	X	X	X[e]	X	X	X	X	X				X	X	X
Height and weight [c],[d]	X							X										
Vital signs [c]	X	X	X	X	X	X	X[e]	X	X	X	X	X				X	X	X
ECOG PS [c],[e]	X	X	X	X	X	X	X	X	X	X	X	X				X	X	X
SpO_2																		
Hematology [c],[e]	X	X	X	X	X	X	X	X	X	X	X	X				X	X	X
Chemistry [c],[e]	X	X	X	X	X	X	X	X	X	X	X	X				X	X	X
Coagulation test [c],[e]	X	X	X	X	X	X	X	X	X	X	X	X				X	X	X
Immunoserological test [c],[e]	X							X										
Viral test [c],[e]	X[f]							X[f]										
Urinalysis [c],[e]	X	X						X	X							X		
Electrocariography																		
CT, MRI, PET							X[h]											
Pregnancy test																		
12-lead resting electrocardiography [c],[e]	X							X										
Bone marrow examination							X[i] BMA4											
Cerebrospinal fluid examination							X[j]											
Blood MTX concentration													X[l]	X[m]	X[n]			
Plasma asparaginase activity	*See Table 8.22-1.																	
Immunogenicity (anti-antibodies)	*See Table 8.22-2.																	
Adverse events	←																	→
Review of concomitant medications and therapies, supportive care	←																	→

[redacted]

Table 8-3 Schedule for Study Procedures in Early Consolidation Therapy and Subsequent Therapies (HR) (Continued)

	HR1							III+L									IM		
	Week 18					Week 19	Week 20	Week 21 Week 31 Week 41		Week 22 Week 32 Week 42		Week 23 Week 33 Week 43		Week 24 Week 34 Week 44		Week 25 Week 35 Week 45	Week 26 Week 36	Week 27 to Week 30 Week 37 to Week 40	Treatment completion/ discontinuation or study discontinuation [q]
Day [a]	1	2	3	4	7	8 [k]	15 [k]	1	2	8	13	15	16	22	27	29 [k]	1	8,15,22,29 [o]	
Criteria for starting treatment [b]	X							X				X					X		
Symptoms and findings [c]	X				X	X	X	X	X	X		X		X		X	X	X [p]	X [r]
Height and weight [c],[d]								X									X		X [r]
Vital signs [c]	X				X	X	X	X	X	X		X		X		X	X	X [p]	X [r]
ECOG PS [c],[e]	X				X	X	X	X	X	X		X		X		X	X	X	X [r]
SpO_2																			X [r]
Hematology [c],[e]	X				X	X	X	X	X	X		X		X		X	X	X	X [r]
Chemistry [c],[e]	X				X	X	X	X	X	X		X		X		X	X	X	X [r]
Coagulation test [c],[e]	X				X	X	X	X	X	X		X		X		X	X	X	X [r]
Immunoserological test [c],[e]								X									X		X [r]
Viral test [c],[e]								X [f]									X [f]		X [f],[r]
Urinalysis [c],[e]					X			X	X								X		X [r]
Electrocariography																			X [r]
CT, MRI, PET																			
Pregnancy test																			X [r]
12-lead resting electrocardiography [c],[e]								X									X		X [r]
Bone marrow examination																			
Cerebrospinal fluid examination																			
Blood MTX concentration		X [l]	X [m]	X [n]															
Plasma asparaginase activity	*See Table 8.22-1.																		
Immunogenicity (anti-antibodies)	*See Table 8.22-2.																		
Adverse events	← →																		
Review of concomitant medications and therapies, supportive care	← →																		

a) If treatment is postponed, the relevant rest schedule will also be postponed.
b) Laboratory results obtained within 4 days before the prescribed day may be used to assess subjects for the starting criteria related to hematology or chemistry.
c) To be performed before the start of the administration of SHP674 or the backbone therapy drugs that are listed in Section 7.2.1 (Backbone Therapy Drugs Used in This Study).
d) Height and weight are allowed to be measured within 7 days before the prescribed day, except for those at treatment completion, treatment discontinuation, or study discontinuation.
e) Laboratory tests are allowed to be performed within 4 days before the prescribed day, except for those at treatment completion, treatment discontinuation, or study discontinuation.
f) If the subject is negative for HBs antigen and positive for HBc antibody or HBs antibody, HBV DNA will be measured to confirm that the result is negative. HBV DNA measurement other than that at screening will not be required for subjects with a documented history of HBV vaccination.
g) When SHP674 administration is resumed after interruption, the same tests as scheduled for Day 38 (except urinalysis) should be performed before administration. If SHP674 is administered on Day 43, 50, or 57, the tests scheduled for that day may be substituted for the tests before administration.
h) As a general rule, PET should be performed in the fasting state.
[redacted]
j) To be performed during the period from Day 59 of I_B/ I_B+L to before the start of consolidation therapy (M2/M5/HR3). If the day of TIT is changed for a social reason such as that the prescribed day falls on a weekend or holiday, the day of bone marrow examination may also be changed accordingly.
k) Tests and assessments can be omitted if the investigator or subinvestigator considers unnecessary. If not omitted, these tests and assessments are allowed to be performed within 4 days before the prescribed day.
l) To be performed 24 hours after the administration of MTX.
m) To be performed 42 and 48 hours after the administration of MTX. Measurement at 36 hours is optional.
n) To be performed 66 hours after the administration of MTX. Measurement at 54 hours is optional.
o) Tests and assessments on IM Day 29 can be omitted if the investigator or subinvestigator considers unnecessary. If not omitted, these tests and assessments are allowed to be performed within 4 days before the prescribed day.
p) The assessment is allowed to be performed within 4 days before the prescribed day.
q) To be performed 30 (+7) days after the last dose of investigational product.
r) If the subject's next therapy starts 30 (+7) days after the last dose of investigational product or earlier, the assessment may be performed during the period from 7 days before the start date of the next therapy to before the start of the next therapy.

8.1 Screening

Subjects will undergo screening after giving informed consent. Screening test items are presented in Table 8.1-1. Screening tests should be conducted within 14 days before enrollment. For subjects who have undergone screening within 3 days before Day 1, duplicated test items can be omitted on Day 1 pre-dose.

Test results obtained before informed consent but within 14 days before enrollment (within 28 days before enrollment for imaging examinations) can be used as screening test results after getting consent from the subject (or the subject's legally acceptable representative).

Table 8.1-1 Screening Test Items

Demographics	Date of written informed consent, sex, date of birth, race, concurrent diseases, medical history, time of diagnosis of the primary disease, genetic analysis results related to the primary disease, chromosome analysis results related to the primary disease, date of enrollment, assessment for the inclusion and exclusion criteria
Disease assessment	Risk classification
Physiological examination	Height, weight, vital signs (blood pressure, pulse rate, temperature, percutaneous arterial oxygen saturation [SpO_2]), ECOG PS
Hematology	RBC, Hb, Ht, WBC, Baso, Eosino, Lymph, Mono, Neutro, lymphoblast count, PLT
Chemistry	AST, ALT, T-Bil, D-Bil, ALP, LDH, γ-GTP, Cr, BUN, TP, Alb, UA, Glu, T-Cho, TG, AMY, lipase, CRP, Na, K, Cl, P, Ca
Coagulation test	Prothrombin time-INR, APTT, fibrinogen, protein S activity, antithrombin activity, D-dimer, FDP
Immunoserological test	IgG, IgA, IgM
Viral test	HIV antibody, HBs antigen, HBs antibody, HBc antibody, HBV DNA*, HCV antibody
Urinalysis	Qualitative urinalysis (protein, glucose, ketone bodies, urobilinogen, occult blood)
Imaging examination	Echocardiography, 12-lead resting ECG, MRI*, PET*, CT
Other tests	Pregnancy test*
Genetic testing	Nudix hydrolase 15 (NUDT15) codon 139 polymorphism analysis

* To be performed as necessary. (See Section 8.12 for HBV DNA, Section 8.14 for MRI and PET, and Section 8.17 for pregnancy test.)

8.2 Subject Demographics

The following information will be entered into the eCRF:

- Date of written informed consent
- Sex
- Date of birth
- Race
- Concurrent diseases
- Medical history
- Time of diagnosis of the primary disease
- Genetic analysis results related to the primary disease (*KMT2A-AFF1* [*MLL-AF4*])
- Chromosome analysis results related to the primary disease (hypodiploid)
- Date of enrollment
- Eligibility based on the inclusion and exclusion criteria

Time point: Screening. Genetic analysis and Chromosome analysis results related to the primary disease should be obtained before risk determination (see Section 3.1.3.1).

8.3 Disease Assessment and Risk Classification

The following assessments will be performed to determine the risk category after the start of study treatment. The results of the assessments will be entered into the eCRF.

8.3.1 NCI Classification

Assessment item: NCI classification

Time points: Screening

8.3.2 Identification of Chimeric Gene Analysis Results

Assessment item: *KMT2A-AFF1* (*MLL-AF*4)

Time points: Before Day 22 of I_A2/I_A4

8.3.3 Identification of Chromosome Analysis Results

Assessment item: Hypodiploid

Time points: Before Day 22 of I_A2/I_A4

8.3.4 Assessment of Response to PSL

Assessment item: Circulating lymphoblast count

Time points: I_A2/I_A4 Day 8

8.3.4.1 Definition of Response to PSL

MTX alone will be administered intrathecally on the first day of the pre-treatment phase (Day 1), and oral administration (or IV administration at the same dose) of PSL will be started on the same day. A subject who has a circulating leukemic cell count (lymphoblast count) of <1000/μL on Day 8 is defined as a prednisolone good responder (PGR). A subject who has a circulating leukemic cell count (lymphoblast count) of ≥1000/μL on Day 8 is defined as a prednisolone poor responder (PPR). Circulating leukemic cell count will be calculated by multiplying circulating white blood cell count (/μL) measured on the same day by the percentage of leukemic cells (%). Results of smear microscopy at each investigative site will be used to determine the response to PSL. A total dosage of PSL of ≥210 mg/m^2 is required to determine the response to PSL. The test required for the determination of PSL response should be performed before the start of administration of the investigational product or backbone therapy drugs listed in Section 7.2.1 (Backbone Therapy Drugs Used in This Study).

8.3.5 Identification of Bone Marrow Examination Results

Assessment items: BMA2, BMA3

Time points: BMA2, I_A2/I_A4 Day15; BMA3, within 7 days from I_A2/I_A4 Day33

Points to note regarding bone marrow aspiration are provided in Section 8.18.

8.4 Symptoms and Findings

Assessment items: Changes in symptoms and findings after the start of study treatment, the presence or absence of new symptoms and findings.

Time points: Screening; once a week from Day 1 of each treatment phase; before SHP674 administration; at the time of treatment completion, treatment discontinuation, or study discontinuation

8.5 Height, Weight

Test items: Measurement of height and weight

Time points: Screening; I_p Day 1; I_A2/I_A4 Day 8; I_B/I_B+L Day 36; Day 1 of each treatment phase after consolidation therapy; at the time of treatment completion, treatment discontinuation, or study discontinuation

8.6 Vital Signs and ECOG PS

Test items: Temperature (°C), blood pressure (mm Hg), pulse rate (beat/minute), ECOG PS

Axillary temperature will be measured. As a general rule, blood pressure (systolic and diastolic) and pulse rate will be measured at rest in the sitting position. Subjects' performance status will be recorded according to the ECOG PS (see Attachment 4 to the protocol [supplement]).

Time points: Screening; once a week from Day 1 of each treatment phase; before SHP674 administration; at the time of treatment completion, treatment discontinuation, or study discontinuation

8.7 Percutaneous Arterial Oxygen Saturation (SpO_2)

Test item: SpO_2

Time points: Screening and at treatment completion, treatment discontinuation, or study discontinuation

8.8 Hematology

Test items: RBC, Hb, Ht, WBC, Baso, Eosino, Lymph, Mono, Neutro, lymphoblast count, PLT

Time points: Screening; once a week from Day 1 of each treatment phase; before SHP674 administration; at the time of treatment completion, treatment discontinuation, or study discontinuation

8.9 Chemistry

As a general rule, chemistry will be performed in the fasting state (at least 2 hours after a meal).

Test items: AST, ALT, T-Bil, D-Bil, ALP, LDH, γ-GTP, Cr, BUN, TP, Alb, UA, Glu, T-Cho, TG, amylase, lipase, CRP, Na, K, Cl, P, Ca, corrected Ca*

* Corrected Ca will be calculated according to the following formulas based on the observed Ca and albumin levels:

- If albumin level is <4.0 g/dL:
  Corrected Ca = Observed Ca level (mg/dL) − albumin level (g/dL) + 4.0
- If albumin level is ≥4.0 g/dL:
  Corrected Ca = Observed Ca level (mg/dL)

Time points: Screening; once a week from Day 1 of each treatment phase; before SHP674 administration; at the time of treatment completion, treatment discontinuation, or study discontinuation

8.10 Coagulation Test

Test items: Prothrombin time-INR, APTT, fibrinogen, protein S activity*, antithrombin activity, D-dimer, FDP

* Protein S activity will be measured only at screening.

Time points: Screening; once a week from Day 1 of each treatment phase; before SHP674 administration; at the time of treatment completion, treatment discontinuation, or study discontinuation

8.11 Immunoserological Test

Test items: IgG, IgA, IgM

Time points: Screening; start day of each treatment phase (including I_A2/I_A4 Day 8 and I_B/I_B+L Day 36); at the time of treatment completion, treatment discontinuation, or study discontinuation

8.12 Viral Test

Test items: HIV antibody, HBs antigen, HBs antibody, HBc antibody, HCV antibody, HBV DNA*

Time point: Screening

* If the subject is negative for HBs antigen and positive for HBs antibody or HBc antibody at screening, HBV DNA will be measured to confirm that the result is negative (<20 IU/mL [1.3 LogIU/mL]). Subsequently, HBV DNA will be measured for the subject on the start day of each treatment phase**, except for the pre-treatment phase and remission induction therapy, and at the time of treatment completion, treatment discontinuation, or study discontinuation to confirm that the result is negative. If the subject has a documented history of HBV vaccination, HBV DNA measurement will not be required, except for at screening.

** To be measured only on Day 1 of HR3 in consolidation therapy for HR.

8.13 Urinalysis

Test items: Qualitative urinalysis (protein, glucose, ketone bodies, urobilinogen, occult blood)

Time points: Screening; once a week from Day 1 of remission induction therapy; before SHP674 administration; Day 1 of each treatment phase after early consolidation therapy; at the time of treatment completion, treatment discontinuation, or study discontinuation

8.14 CT, MRI, and PET

As a general rule, PET should be performed in the fasting state.

Detailed conditions for image assessment will be specified in a written procedure developed elsewhere.

Test item: CT, MRI, PET

Time point: [redacted]

8.15 Twelve-lead Resting Electrocardiography

Test items: Heart rate, PR interval, QRS duration, QT interval, QTc intervals (QTcF, QTcB)

*The QTc intervals (QTcF, QTcB) will be automatically calculated on the electronic case report form according to the following formulas:

$QTcF\ (msec) = QT\ interval/(60/heart\ rate)^{1/3}$

$QTcB\ (msec) = QT\ interval/(60/heart\ rate)^{1/2}$

Standard 12-lead ECG will be performed at rest in the decubitus position to determine the presence or absence of findings. If there are any findings, whether they are clinically significant or not will be determined, and the interpretation of clinical significance and the nature of the findings will be entered into the eCRF. During remission induction therapy, the ECG will be recorded before SHP674 administration,

immediately after SHP674 administration, and 11 days after the end of SHP674 administration using measurement equipment available at the investigative site 3 consecutive times at 1- to 2-minute intervals, after approximately 5-minute rest in the decubitus position. Drug concentration measurement that is scheduled for the same time point as ECG recording must be performed after ECG. ECG recording immediately after SHP674 administration and 11 days after the end of SHP674 administration should be performed before the start of administration of investigational product or the backbone therapy drugs listed in Section 7.2.1 (Backbone Therapy Drugs Used in This Study) on the same day.

Time points: Screening; remission induction therapy (see Table 8.15-1); Day 1 of each treatment phase after early consolidation therapy; at the time of treatment completion, treatment discontinuation, or study discontinuation

Table 8.15-1 ECG Measurement Schedule in Remission Induction Therapy (SR/IR/HR)

Time Points		Allowance
Remission induction therapy (I_A2/I_A4)	Before SHP674 administration	One day to 15 minutes before administration, and before drug concentration measurement
	Immediately after the end of SHP674 administration	From the last dose of SHP674 to before drug concentration measurement
	11 days after the end of SHP674 administration	±1 day and before drug concentration measurement

8.16 Echocardiography

Test item: LVEF

Time point: Screening, at the time of treatment completion, treatment discontinuation, or study discontinuation

8.17 Pregnancy Test

The presence or absence of menstruation, menstrual cycle, surgical history, and other relevant information will be obtained through interview. Women of childbearing potential (a woman of childbearing potential is defined as a woman who has experienced her first menstruation, has not undergone hysterectomy, bilateral tubal ligation, or bilateral ovariectomy and is not postmenopausal. Postmenopausal status is defined as amenorrhea of ≥12 consecutive months with no specific causes) will undergo a pregnancy test.

Test item: Serum or urine hCG

Time point: Screening, at the time of treatment completion, treatment discontinuation, or study discontinuation

8.18 Bone Marrow Examination

Test items: NCC, proportion of lymphoblasts

Time points:

BMA2: ±1 day from I_A2/I_A4 Day 15

BMA3: Within 7 days after the end of administration on Day 33 of I_A2/I_A4

BMA4: From $I_{B/}$ I_B+L Day 65 to before the start of consolidation therapy (M2/M5/HR3)

8.18.1 Bone Marrow Aspiration during Remission Induction Therapy: Points to Note for BMA2

On Day 15 of I_A2/I_A4, VCR and DNR should be administered after the completion of BMA2. If Day 15 of I_A2/I_A4 falls on a national holiday or a weekend, BMA2 can be performed ±1 day of Day 15. However, if BMA2 is performed on Day 16 of I_A2/I_A4, the administration of VCR and DNR on Day 15 should also be shifted to Day 16..

8.18.2 Bone Marrow Aspiration after the End of Remission Induction Therapy: Points to Note for BMA3

Bone marrow aspiration at the end of remission induction therapy (I_A2/I_A4) should not necessarily be performed on Day 33 of I_A2/I_A4, since a certain level of bone marrow recovery is required to perform the aspiration. It can be performed later than Day 33 if bone marrow recovery appears to be delayed. On the other hand, the criteria for starting early consolidation therapy (I_B/I_B+L) is "neutrophil count ≥500/μL and platelet count ≥50000/μL." Both of the above criteria are based on the conditions that the subject is not receiving G-CSF or received the last dose of G-CSF at least 48 hours before and that the subject received the last platelet transfusion at least 3 days before. It is necessary to perform bone marrow aspiration at an appropriate time focusing on minimizing the transition period from remission induction therapy (I_A2/I_A4) to early consolidation therapy (I_B/I_B+L) as much as possible. Therefore, there may be some subjects who meet the criteria for starting early consolidation therapy (I_B/I_B+L) [redacted] Subjects who do not meet the criteria for starting early consolidation therapy (I_B/I_B+L) for 7 days after the end of remission induction therapy (I_B/I_B+L) will undergo a bone marrow examination. Subjects with ≥5% blasts will start early consolidation therapy once white blood cell count increases to ≥1000/μL. Subjects with <5% blasts will start early consolidation therapy once neutrophil count increases to ≥500/μL and platelet count increases to ≥50000/μL. Thus, all subjects must undergo bone marrow aspiration at least once within 7 days after the end of administration on Day 33 of I_A2/I_A4. If it is difficult to determine whether the subject can start the next therapy 7 days after the end of administration on Day 33 of I_A2/I_A4 (for example, the presence of blasts is suspected but not evident because of hypocellular bone marrow), an additional bone marrow examination will be performed when white blood cell count has increased to around 1000/μL to immediately start early consolidation therapy.

8.18.3 Bone Marrow Aspiration after the End of Early Consolidation Therapy: Points to Note at BMA4

All subjects will be assessed for remission by bone marrow aspiration (BMA4) at the end of early consolidation therapy (I_B/I_B+L). Remission should be assessed under the conditions that the subject is not receiving G-CSF or received the last dose of G-CSF at least 48 hours before the assessment and that the subject received the last platelet transfusion at least 3 days before the assessment. [redacted]

8.19 Cerebrospinal Fluid Examination

Test items: Cell counts (WBC and RBC), lymphoblast count, CNS status

Time points: I_p Day 1 (the examination is to be performed simultaneously with MTX IT. However, it can be postponed until up to Day 4, if a subject cannot receive MTX IT for a reason such as that the subject's initial visit falls on a weekend), from Day 33* of I_A2/I_A4 to before the start of early consolidation therapy (I_B/I_B+L), from I_B/I_B+L Day 59* to before the start of consolidation therapy (M2/M5/HR3).

* If the day of TIT is changed for a social reason such as that the prescribed day falls on a weekend or holiday, the day of cerebrospinal fluid examination may also be changed accordingly.

8.20 Blood MTX Concentration

Test item: Blood MTX concentration

Time points: As specified below for each risk category.

SR and IR: M2 Days 9, 10, 11, 23, 24, 25, 37, 38, 39, 51, 52, and 53

HR: HR2 Days 2, 3, and 4; HR1 Days 2, 3, and 4

8.21.2 Evaluation of CNS Involvement

CNS remission is defined as achievement of CNS-1 status in a subject with CNS-2 status. CNS relapse is defined as new development of CNS-3 status or clinical signs of CNS leukemia such as facial nerve palsy, brain/eye involvement, or hypothalamic syndrome.

8.21.3 Evaluation of Extramedullary Disease

Extramedullary disease will be evaluated by contrast-enhanced CT (neck, chest, abdominal, or pelvic). PET, biopsy, and other tests will be performed if a false-positive result is suspected on CT and the investigator or subinvestigator judges it necessary. The response criteria presented in Table 8.21.3-1 will be used for evaluation.

Table 8.21.3-1 Response Criteria for Mediastinal Disease[18]

PR	>50% decrease in the sum of the products of the greatest perpendicular diameters (SPD) of the mediastinal enlargement. At least one of the previously observed lesions is positive on post-treatment PET for subjects who had a positive result on previous PET.
PD	>25% increase in the SPD of the mediastinal enlargement. At least one of the previously observed lesions is positive on post-treatment PET for subjects who had a positive result on previous PET.
No response (NR)	Failure to qualify for PR or PD.

8.22 Plasma Asparaginase Activity and Anti-Drug Antibodies

8.22.1 Plasma Asparaginase Activity

Test items: Plasma asparaginase activity

Time points: As shown in Table 8.22.1-1 below.

Table 8.22.1-1 Time Points for Measurement of Plasma Asparaginase Activity (SR/IR/HR)

Time Points		Allowance
Remission induction therapy (I_A2/I_A4)	Before the start of SHP674 administration	One day before administration to 15 minutes before administration
	5 minutes after the end of SHP674 administration	−2 to 10 minutes
	4 hours after the end of SHP674 administration	±10 minutes
	24 hours after the end of SHP674 administration	±1 hour
	48 hours after the end of SHP674 administration	±2 hours
	4 days after the end of SHP674 administration	±4 hours
	11 days after the end of SHP674 administration	±1 day
	14 days after the end of SHP674 administration	±1 day
	18 days after the end of SHP674 administration	±2 days
	25 days after the end of SHP674 administration	±2 days
Re-induction therapy-1 (III/III+L) Re-induction therapy-2 (III/III+L)	Before the start of SHP674 administration	One day before administration to 15 minutes before administration
	11 days after the end of SHP674 administration	±1 day
	14 days after the end of SHP674 administration	±1 day
	25 days after the end of SHP674 administration	±2 days
Treatment completion, treatment discontinuation, or study discontinuation	At treatment completion, treatment discontinuation, or study discontinuation	30 (+7) days after the last dose of investigational product or from 7 days before the start date of next therapy to before the start of the next therapy, whichever is earlier.

Asparaginase activity will be determined using a coupled enzymatic activity assay, validated according to current regulatory guidelines.

8.22.2 Anti-Drug Antibodies

Test items: Presence or absence of the production of ADA

Time points: As shown in Table 8.22.2-1 below.

Table 8.22.2-1 Time Points for Immunogenicity Measurements (SR/IR/HR)

Time Points		Allowance
Remission induction therapy (I_A2/I_A4)	Before the start of SHP674 administration	One day before administration to 15 minutes before administration
	25 days after the end of SHP674 administration	±2 days
Re-induction therapy-1 (III/III+L)	Before the start of SHP674 administration	One day before administration to 15 minutes before administration
Re-induction therapy-2 (III/III+L)	Before the start of SHP674 administration	One day before administration to 15 minutes before administration
Treatment completion, treatment discontinuation, or study discontinuation	At treatment completion, treatment discontinuation, or study discontinuation	30 (+7) days after the last dose of investigational product or from 7 days before the start date of next therapy to before the start of the next therapy, whichever is earlier.

Immunogenicity assessments will include the detection of binding antibodies against the study drug (SHP674) as well as those antibodies that bind to PEG in samples taken during the study.

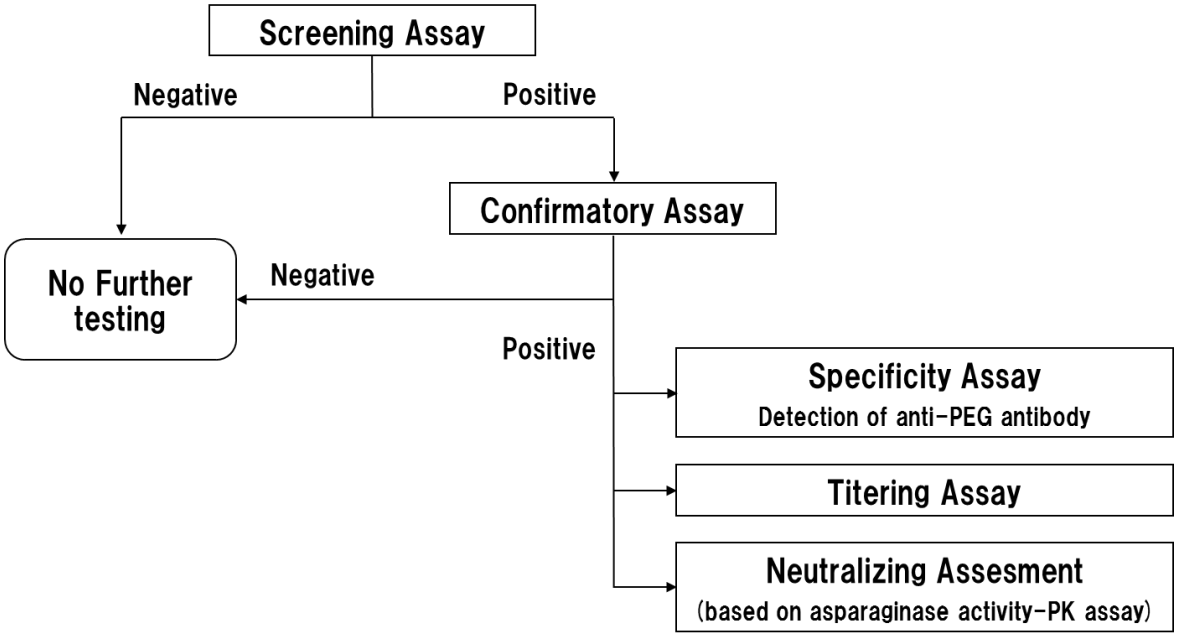
This evaluation will be based on qualitative enzyme-linked immunosorbent assays (ELISA) using SHP674 as coating antigen. All positive samples will be further confirmed by competitive ELISA for the presence of binding antibodies against SHP674. Samples, confirmed positive, will then be assayed for antibodies against PEG. For all these assays, antibody status (negative or positive) will be reported.

The antibody positive samples will be further diluted and tested, and the highest sample dilution with a positive result will be reported as the anti-drug antibody titer.

In the absence of a validated neutralizing antibody assay, the neutralizing potential of anti-drug antibodies in positive samples will be evaluated based on the concomitant results of the asparaginase activity assay.

All assays are validated with respect to cut-point, precision, linearity, short-term stability, freeze-thaw stability and drug interference.

Figure 8.22.2-1 Flow of Immunogenicity Measurements



8.23 Number and Volume of Blood Sampling

The number of blood sampling for tests specified for this study is at least 52. The volume of blood sampling will be maximum 25.4 mL per day (the volume can be determined by each investigative site according to the body constitution of each subject) for hematology, chemistry, coagulation test, immunoserological test, and viral test; and maximum 2.5 mL per sampling for the assessments of plasma asparaginase activity and the production of ADA. However, the number and volume of blood sampling may increase if retests are required. For subjects with a body weight of <5.5 kg, the time points and volume of blood sampling for the assessments of plasma asparaginase activity and ADA production will be determined in consultation with the Sponsor.

8.24 Survival Follow-up

The investigator or subinvestigator will follow subjects for survival at the following time point:

Investigation items: Date of death, cause of death, causal relationship between death and investigational product, information on post-study treatment, presence or absence of relapse, date of relapse, presence or absence and date of occurrence of second malignancy (including myelodysplastic syndrome), date of last survival update

Time point: 365 (±7) days after the start of SHP674 administration in remission induction therapy.

8.25 Genetic Testing

8.25.1 Test Item

NUDT15 codon 139 polymorphism analysis

8.25.2 Purpose of Testing and Relation to the Study

NUDT15 is an enzyme involved in the metabolism of thiopurine drugs such as 6-MP that are used for the treatment of ALL. Patients who have the Cys/Cys homozygous genotype of the NUDT15 codon 139 have been reported to experience serious adverse reactions (e.g., severe leukopenia and alopecia universalis) early after the start of treatment with thiopurine drugs such as 6-MP, because the enzyme activity of NUDT15 is significantly reduced in these patients.[20] In consideration of the safety of subjects, the NUDT15 codon 139 polymorphism analysis will be conducted in this study to adjust the dose of 6-MP according to the genotype determined.

8.25.3 Target Population, Time of Testing, Handling of Samples Collected

Peripheral blood (2.0 mL) will be collected at screening from all subjects who provide consent to participate in the study. Since this testing has already been listed on the national health insurance coverage list in Japan, blood will be collected according to the procedure of each investigative site or laboratory and immediately tested. The Sponsor or in-country caretaker will not store blood samples collected from subjects or DNA samples extracted from subjects' blood; these samples will be discarded as soon as the testing is completed, according to the procedure of each investigative site or laboratory.

8.25.4 Genomic Analysis Method

DNA will be extracted from blood collected. The NUDT15 codon 139 genotype will be determined by the real-time PCR method.

8.25.5 Anonymization of Samples

To protect subjects' privacy, samples will be anonymized according to the procedure of each investigative site and laboratory.

8.25.6 Procedure for Obtaining Informed Consent

An explanation about the NUDT15 codon 139 polymorphism analysis will be provided and consent for the analysis will be obtained, simultaneously at the time of informed consent discussion for the study. Since this testing will be conducted in all subjects who participate in the study, subjects who do not give consent for the testing cannot participate in the study.

8.25.7 Actions to Be Taken in the Case of Consent Withdrawal

If a subject or legally acceptable representative withdraws consent for the testing, the investigative site will promptly notify it to the Sponsor and take appropriate actions to discard the blood samples or extracted DNA samples of the subject. If the results of the NUDT15 codon 139 polymorphism analysis cannot be obtained from a subject because of consent withdrawal, or if a subject or legally acceptable representative withdraws consent for the use of analysis results after they are obtained, the subject will be withdrawn from the study according to Section 5.1.1 Withdrawal from the Study or Section 5.1.2 Treatment Discontinuation.

8.25.8 Disclosure of Genotype to Subjects

As a general rule, information on the NUDT15 codon 139 genotype will be disclosed by the investigator or subinvestigator to the subject or legally acceptable representative (if the subject's legally acceptable representative has given informed consent to participate in the study). The results of the NUDT15 codon 139 polymorphism analysis will be documented on medical records and other relevant documents and retained.

8.25.9 Other Points to Note

If the genotype determined by the NUDT15 codon 139 polymorphism analysis is Cys/Cys or heterozygous, the dose of 6-MP should be changed according to Section 7.2.3 Criteria for Changes in Treatment with Each Backbone Therapy Drug.

If it takes time to obtain the results of the analysis, the subject can be enrolled with no data at screening. In that case, the data must be obtained before the first dose of 6-MP.

9 Adverse Events

9.1 Definition of Adverse Events

An adverse event (AE) is herein defined as any untoward medical occurrence in a subject after signing informed consent. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease, whether or not it is related to the investigational product. Worsening during the study of a symptom or disease already present when the subject entered the study (increase in frequency and/or intensity) also constitutes an adverse event. A treatment-emergent adverse event (TEAE) is defined as any untoward medical occurrence in a subject who received an investigational product which occurs during the period from Day 1 of the pre-treatment phase to 30 (+7) days after the last dose of investigational product, or until the start of a new therapy, whichever occurs first. A drug-related TEAE is defined as an AE for which a causal relationship to investigational product is assessed as "related." The worsening of the primary disease (including concurrent conditions) or PS needs not to be regarded as a AE.

Results of laboratory tests will be checked against the reference range at the investigative site for any deviations (abnormal test results). Any abnormal test results will be compared with those obtained before the start of study treatment to determine whether or not such a change is clinically significant (abnormal change).

When any abnormal changes in signs, symptoms, or laboratory data associated with a disease (diagnosis) are reported, the underlying disease or diagnosis will be recorded as AEs. However, any individual atypical or extremely severe signs or symptoms of the disease will be regarded as independent AEs, separately from the diagnosis.

Adverse events will be collected from the time of signing the informed consent to 30 (+7) days after the last dose of investigational product. In the screening period, any event that the investigator considers associated with a procedure, change or withdrawal of previous/concomitant treatment relating to the conditions of the protocol, or a product other than the test drug, taken as part of the protocol will be recorded as adverse events; all others may be recorded as past medical history.

Note: Serious AEs that are deemed by the investigator to be related to investigational product or to study procedures or conduct may be reported irrespective of the time of onset after the end of the study.

9.2 Assessment Items

The following information will be recorded on the eCRF.

AEs will be followed up until the subject recovers to the baseline status or until the investigator or subinvestigator judges that no further follow-up is necessary, based on symptoms, findings, and laboratory data, among other conditions. Information collected during the period from informed consent to 30 (+7) days after the last dose of investigational product, will be entered into the eCRF. Any actions taken during follow-up with respect to the AE will be recorded on the eCRF.

1) Reported term for the adverse event
2) Start date of adverse event
3) Severity (standard toxicity grade): As described in Section 9.2.1.

4) Seriousness (serious event)
   - Serious (Yes): AEs defined in Section 9.2.3.
   - Non-serious (No): AEs other than those defined in Section 9.2.3.
5) Action taken for SHP674 or other investigational products
   - Dose not changed
   - Dose reduced
   - Drug interrupted
   - Drug withdrawn
   - Not applicable
6) Other action taken
   - None
   - Other drug taken/Other therapy provided
   - Other
7) Outcome of adverse event
   - Recovered/resolved
   - Recovering/resolving
   - Not recovered/not resolved
   - Recovered/resolved with sequelae
   - Fetal
   - Unknown
8) End date of adverse event
9) Relationship to SHP674 or other investigational products

   A causal relationship to investigational product will be determined according to the following 2 categories (see Section 9.2.2).
   - Related
   - Not related

9.2.1 Severity Assessment

The severity of all AEs will be determined according to CTCAE version 5.0, and the worst grade will be recorded:

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) (preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.).

Grade 3: Severe or medically significant but not immediately life-threatening (Severe); hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL (bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).

Grade 4: Life-threatening; urgent intervention indicated.

Grade 5: Death related to a AE (fatal)

9.2.2 Assessment of Causal Relationship with Study Treatment

A causal relationship with study treatment is categorized as either of the following:

Related: There is a reasonable causal relationship between study treatment and an AE.

Not related: There is no reasonable causal relationship between study treatment and an AE.

Whether there is a "reasonable causal relationship" or not should be determined comprehensively by considering the following points:

- Recurrence of the event after rechallenge: The AE occurs again when the administration of the investigational product is resumed after dosing or drug interruption.
- No doubt: An evident causal relationship has been established.
- Reasonable time of onset: Time to the onset of the AE is reasonable to explain the causal relationship.
- Disappearance of the event after stopping administration: The AE improves or recovers after dosing interruption, discontinuation, or dose reduction.
- No confounding risk factors: There are no other possible risk factors, and the occurrence of the AE can be predicted based on the pharmacological property of the investigational product.
- Exposure and duration of exposure are explainable in view of the causal relationship: There is no contradiction between the onset of the AE and actual dose and duration of administration of the investigational product in view of the known mechanism of the investigational product.
- Medical history is accurate enough to support the causal relationship: The subject has never experienced the AE before the start of study treatment.
- A causal relationship can be evidently determined: A causal relationship can be evidently determined based on information such as results of tests specially performed, the subject's background, and clinical symptoms.
- No other reasonable factors: The onset of the AE cannot be reasonably explained by other factors such as the subject's underlying condition, other medications, or environmental factors.

On the other hand, no "reasonable causal relationship" between the AE and the investigational product is considered to be present in the following circumstances:

- The AE does not meet any of the above conditions.
- There is a rationale such as exposure or reasonable time course, but the AE does not resolve after discontinuation of the investigational product (if discontinued).
- The AE may meet any of the above conditions, but there are other possible causes of the AE.

9.2.3 Definition of Serious Adverse Events

A serious adverse event (SAE) is any event defined as below. Hospitalization for screening and pre-planned hospitalization are not regarded as SAEs. The worsening of the primary disease (including concurrent conditions) or PS needs not to be regarded as an AE even if the conditions specified below are met.

1) Death;
2) Life-threatening;
    - An event in which the subject was at risk of death at the time of the event; not one which hypothetically might have caused death if it were more severe.

3) Hospitalization or prolongation of existing hospitalization;
4) Persistent or significant disability/incapacity (as per reporter's opinion);
   - For example seriously disrupts the ability of the subject to lead a normal life, leads to a persistent or permanent significant change, deterioration, injury or perturbation of the subject's body functions or structure, physical activity and/or quality of life.
5) Congenital anomaly or birth defect; or
6) Other clinically critical conditions
   - Any event that might not be immediately life-threatening or result in death or hospitalization, but might jeopardize the subject or might require intervention to prevent one of these outcomes. The investigator should exercise his/her scientific and medical judgement to decide whether or not such an event requires expedited reporting to the Sponsor.

9.2.4 Other Significant Adverse Events

Other significant AEs are defined as follows:

- Any non-serious AEs that lead to discontinuation of investigational product administration.
- Investigational/non-investigational drug overdose. Must notify the Sponsor immediately after learning of the event.
- Pregnancy: Stop the study treatment immediately upon learning of the event and notify the sponsor immediately.

9.3 Actions to Be Taken for Adverse Events

9.3.1 Treatment of Subjects

If an AE occurs, the investigator or subinvestigator will take appropriate actions such as providing adequate medical care and withdrawal from the study as needed to ensure the safety of the subject.

9.3.2 Emergency Safety Measures

The investigator or subinvestigator will have a responsibility for ensuring the safety of subjects throughout the study procedures. An emergency safety measure is a deviation from or change to the protocol that needs to be conducted by the investigator or subinvestigator without prior approval by the IEC/IRB to avoid immediate hazards to a subject.

The investigator or subinvestigator may take appropriate emergency safety measures to protect subjects from immediate hazards to health or safety. However, **the investigator or subinvestigator must report the measures to the Sponsor or the in-country caretaker immediately after taking such measures.** Any AEs that lead to emergency safety measures must be reported to the parties involved according to the reporting procedure described in Section 9.3.3.

9.3.3 Reporting to Parties Involved

9.3.3.1 Serious Adverse Event

1) If a serious AE occurs, regardless of whether it is related to the investigational product or not, the investigator or subinvestigator will immediately (within 24 hours of first awareness of the event) notify the Emergency Safety Information Center or the Sponsor or in-country caretaker in person, or

by phone, e-mail, or fax (Serious Adverse Event Report Form [Attachment 3 to the protocol [supplement] or a form prescribed by the investigative site should be used).

2) Within 7 days after receipt of the notice, the investigator will submit a detailed written report using the Serious Adverse Event Report Form (Detailed Report) to the Sponsor or in-country caretaker and the director of the investigative site. Serious and unexpected drug-related AEs should be identified when reporting to the director of the investigative site.
3) The investigator will provide additional information as requested by the Sponsor or in-country caretaker, the director of the investigative site, or the IRB.
4) The director of the investigative site will consult with the IRB whether to continue the study at the site.

Emergency Contact

Emergency Safety Information Center
BELLSYSTEM24, Inc.
Tel: [redacted] Fax: [redacted]
Reception hours:24 hours a day, every day of the year

9.3.3.2 Non-Serious Adverse Events

If a noteworthy AE occurs, the investigator or subinvestigator will promptly provide the Sponsor or the in-country caretaker with a description of the event and the action taken. Any other AEs will be reported to the Sponsor or the in-country caretaker at appropriate times.

10 MANAGEMENT OF SUBJECTS

10.1 Notification to Other Departments or Hospitals

Before the start of study treatment, the investigator or subinvestigator will ask the subject if he or she is scheduled to receive medical care or medications at any other department or hospital. If the subject is receiving medical care or medications at other department or hospital, the investigator or subinvestigator will notify the treating physician that the subject will participate in the study. The investigator or subinvestigator will identify the name of any medication the subject has received other than those prescribed by the investigator or subinvestigator as well as how it has been used.

If the subject newly receives medical care or medications at any other department or hospital during the study, the investigator or subinvestigator will take similar actions to the above.

10.2 Instructions to Subjects

The investigator, subinvestigator, or clinical research coordinator provided the following instructions to subjects (or their guardians).

10.2.1 Contraception

The investigator or subinvestigator will instruct subjects to use effective contraception from the day of informed consent to 6 months after the last dose of SHP674 for women of child-bearing potential and from the date of the first dose of SHP674 to 6 months after the last dose of SHP674 for fertile men. Effective contraception is defined as using any two of the following methods: condom, intrauterine contraceptive device, and diaphragm; or avoiding sexual intercourse. The concomitant use of SHP674 and oral contraceptives is not recommended since there is a potential for an indirect interaction between them. The investigator or subinvestigator will thoroughly explain the risks in pregnancy and the effective contraceptive methods to subjects.

Subjects will be instructed to report immediately to the investigator or subinvestigator if a female subject or a partner of a male subject becomes pregnant during the above period. If a female subject becomes pregnant, the investigator or subinvestigator will immediately take appropriate measures such as withdrawing the subject from the study or treatment to ensure safety and will follow up until further observation is considered unnecessary. If a partner of a male subject becomes pregnant, necessary actions such as follow-up will be taken after obtaining voluntary written informed consent (the informed consent form will be developed elsewhere) from the partner.

11 Data Management

11.1 Source Documents

Subjects' data will be obtained from source documents in which the data are originally recorded. Source documents include, but are not limited to, medical records (medical information, previous medications, and concomitant medications are entered in the eCRF based on medical records), clinical and office charts, test and pharmacy dispensing records, diaries, microfiches, X-rays, and correspondence.

All source documents will be handled as confidential information and stored securely. In study-specific documents other than signed written informed assent or consent, subjects will be identified not by name but by a subject identifier or code.

11.2 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

By agreeing with this protocol, the investigator agrees to treat all subject data used and disclosed in connection with this study in accordance with all applicable rules, and regulations for privacy protection, including applicable provisions of the Personal Information Protection Law and their implementing regulations. During monitoring and auditing by the Sponsor or the in-country caretaker, the IRB/IEC's review, and inspections by domestic and foreign regulatory authorities, the investigator and the investigative site should allow them direct access to (and copying of, if required) all study-related records including source documents.

11.3 eCRF

In this study, an electronic data capture (EDC) system will be used for data collection. The EDC system provides each investigative site with the functions of data entry in the eCRF, checking the input data, and responding to inquiries from the Sponsor or the in-country caretaker on the input data, besides the function of electronic signature. The entered data will be encrypted and transferred to the EDC server via the Internet. This EDC system is designed to meet requirements and guidelines of regulatory agencies.

The investigator will fill out an eCRF for each subject and after ascertaining all data to be accurate and complete, append his or her electronic signature through the EDC system. If an eCRF is filled out by a subinvestigator or clinical research coordinator, the investigator will check the accuracy and completeness of data prior to appending his or her electronic signature. The Guide for Changes or Corrections to the Electronic Case Report Form provided by the Sponsor or the in-country caretaker will be followed.

In this study, the subject data stored in the EDC server will be handled as the original eCRF. If the eCRF data are relocated to a non-rewritable medium (e.g., DVD), the eCRF in the medium will be handled as the original. If the eCRF data are relocated to an electronic document management system, the eCRF in the system will be handled as the original. A predefined written procedure will be followed when relocating the data to a non-rewritable medium or the electronic document management system.

The Sponsor or the in-country caretaker will provide a copy of the eCRF and a copy of change or correction history to the investigative site.

By agreeing with this protocol, the investigator agrees to treat all subject data used and disclosed in connection with this study in accordance with all applicable rules and regulations for privacy protection.

The investigator, subinvestigator, or clinical research coordinator will change or correct entries in the eCRF according to the Guide for Changes or Corrections to the Electronic Case Report Form provided by the Sponsor or the in-country caretaker. The change or correction history to the eCRF is automatically recorded on the EDC system.

11.4 Items That Allow Handling of eCRF Entries as Source Documents (Source Data)

The following data may be directly entered into the eCRF and used as source document (source data). In the case that the same information is included in a medical record, the information in the medical record will be handled as source document (source data).

1) AE term, severity, seriousness, action taken, date of outcome identification, causal relationship to investigational product, and comments
2) Reason for use of a concomitant medication or therapy
3) Date of early termination, time of early termination (only during hospitalization), reason for the early termination, action taken, and course of the subject's condition after early termination
4) Special notes in particular other than those above and comments from the investigator or subinvestigator

11.5 QUALITY CONTROL AND QUALITY ASSURANCE OF THE STUDY

The Sponsor or the in-country caretaker will verify, through monitoring and auditing, that the study, data generation, recording, and reporting are being conducted in compliance with the protocol and the Standards for the Implementation of Clinical Trials on Pharmaceutical Products (GCP Ordinance; Ministry of Health and Welfare Ordinance No. 28; 27 March, 1997).

The management and quality assurance of data will be conducted according to the standard operating procedures for clinical studies and auditing of the Sponsor or the in-country caretaker.

The monitor will check and ensure that the study is being conducted in compliance with ICH E6 Guidelines, the protocol, and written procedures for this study and that the entries of the eCRF are consistent with the source document. Detailed procedures will be given in a monitoring plan document developed elsewhere or an alternative written procedure.

12 STATISTICAL ANALYSIS

12.1 Statistical Methods

Efficacy, safety, PK and immunogenicity endpoints to be analyzed and the relevant analysis methods are specified below.

All analyses will be performed separately for Part 1 and Part 2 of study. Analysis of safety, PK, and immunogenicity will be performed by combining data from Part 1 and Part 2 (for subjects receiving the same dose in Part 1 as in Part 2) in addition to analyses performed separately for Part 1 and Part 2.

Unless otherwise specified, categorical data will be summarized using frequencies and percentages, and continuous data will be summarized using descriptive statistics. The descriptive statistics will be the number of subjects, mean, standard deviation, minimum, median, and maximum.

12.1.1 Primary Endpoint

Part 1

The frequencies of all TEAEs and SHP674-related TEAEs that occur or worsen during the tolerability assessment period will be summarized by nature of events, based on the MedDRA PTs and SOCs. A list of the intolerable toxicities that are observed during the tolerability assessment period will be created.

Part 2

The percentage of subjects who have a plasma asparaginase activity of ≥0.1 IU/mL 14 days (336 hours) after the first dose of SHP674 and the corresponding 95% confidence interval will be calculated.

12.1.2 Secondary Endpoints

12.1.2.1 Safety

The frequencies of all TEAEs and SHP674-related TEAEs that occur or worsen after the start of study treatment will be summarized by nature of events based on the MedDRA PTs and SOCs.

All adverse events will be analyzed 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

Descriptive statistics of laboratory parameters and continuous variables of vital signs will be calculated for each time point. Shift tables for qualitative urinalysis results and 12-lead ECG data at baseline and at each time point after the start of administration will be created.

12.1.2.2 PK

The PK parameters shown in the table below will be computed from individual plasma asparaginase activity by noncompartmental analysis using an appropriate validated PK software.

C_{max}	Maximum observed plasma asparaginase activity
T_{max}	Time to maximum plasma asparaginase activity
$T_{1/2}$	Elimination half-life.
AUC_{0-t}	Area under the plasma asparaginase activity-time curve from time zero to the time of the last quantifiable concentration (C_t)
AUC_{0-inf}	Area under the plasma asparaginase activity-time curve from time zero to infinity.
CL	Clearance
Vss	Volume of distribution at steady-state

Descriptive statistics of plasma asparaginase activity and PK parameters (mean, SD, median and [min, max]) will be performed. Plasma asparaginase activity over time will be plotted. This will be performed by a pharmacokineticist.

12.1.2.3 Immunogenicity

Immunogenicity assessments will include the detection of binding antibodies against the study drug (SHP674) as well as those antibodies that bind to PEG in samples taken during the study.

Considering the low number of subjects and the anticipated low rate of seroconversion, results will be reported as follows:

- Pre-existing anti-drug or anti-PEG antibodies: Number of samples confirmed positive at baseline versus total number of baseline samples. If the predose sample at induction is missing, the baseline sample status will be considered negative.
- Seroconversion upon treatment: Number of samples converted from negative at baseline to positive after treatment.

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.

On a case by case approach, the impact of anti-drug and anti-PEG antibodies positive status will be investigated:

- on the pharmacokinetics through the temporal association of antibodies with the loss of asparaginase activity.
- on the safety through the potential relationships with treatment–emergent hypersensitivity and anaphylactic reactions.

12.1.2.4 Efficacy

The 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 overall survival rate and the event-free survival rate (EFS) at 1 year after the start of study treatment will be calculated. Event-free survival is defined as time from the first dose of SHP674 to the date of induction failure, documented relapse, diagnosis of a second malignant neoplasm (including myelodysplastic syndrome), or death from any cause, whichever comes first. In the absence of a documented EFS event as defined above, EFS is to be censored on the date of last evaluation.

[redacted]

12.2 Target Sample Size

Part 1: 3 to 6 evaluable subjects

Part 2: 22 subjects

12.2.1 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,[1,2] and 500 children are newly diagnosed with ALL each year in Japan.[2]

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 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.

12.3 Criteria for Premature Termination of the Entire Study

No criteria for premature termination of the study based on a statistical rationale will be specified.

12.4 Handling of Missing, Unused, and Abnormal Data

If any of the data described in Section 12.1 are missing, the missing data will not be imputed by a specific statistical method unless otherwise specified.

12.5 Development of Statistical Analysis Plan and Procedure for Reporting Deviations from the Original Statistical Analysis Plan

The statistical analysis plan (SAP) will be prepared prior to first patient enrolled and any subsequent amendments will be documented, with final amendments completed prior to CRF database lock at the end of remission induction therapy.

12.6 Selection of Subjects to be Included in Analyses

The following sets are defined as analysis sets.

12.6.1 All Enrolled Set

The all Enrolled set will consist of all patients who have provided informed consent in the study.

12.6.2 Safety Analysis Set

The safety analysis set 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 the Part 1 will be based on the safety analysis set .

12.6.3 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 study. All efficacy analyses (including primary analysis) in Part 2 will be based on the Full Analysis Set.

12.6.4 Immunogenicity Analysis Set

The immunogenicity analysis set 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 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 study as well as for the combination of Parts 1 and 2 resulting in all patients dosed in the study.

12.6.5 PK Analysis Set

The PK analysis set is defined as all subjects enrolled in Part 1 or Part 2 who have received first dose of SHP674 at remission induction therapy and are evaluable for non-compartmental analysis. The PK analysis set 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.

12.7 Data Cut Off

A snapshot of data will be taken for analysis of all available endpoints after all subjects completed remission induction therapy. The primary analysis of the study will be performed after all patients complete remission induction therapy. The clinical study report (CSR) will be based off of the data from the period of remission induction phase.

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.

13 ETHICAL CONSIDERATIONS

13.1 Compliance with GCP and the Protocol

This study will be conducted based on the principles described in the Declaration of Helsinki and in compliance with the Pharmaceuticals and Medical Devices Act, "Standards for the Implementation of Clinical Trials on Pharmaceutical Products" (Ministry of Health and Welfare Ordinance No. 28; 27 March, 1997) and the partial revision of the Ordinance, the Personal Data Protection Law, "Guidelines on Genomic Sampling and Management of Genomic Data" (Notification No. 0118-1 of the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare; 18 January, 2018), "Studies Utilizing Pharmacogenomics" (Notification No. 0930007 of the Evaluation and Licensing Division, Pharmaceutical and Medical Safety Bureau, Ministry of Health and Welfare; 30 September, 2008), "Ethical Guidelines for Medical and Health Research Involving Human Subjects" (Ministry of Education, Culture, Sports, Science and Technology, Ministry of Health, Labour and Welfare, and Ministry of Economy, Trade and Industry; 25 November, 2014 [partial revision]), and "Points to Consider in Collecting Genomic Samples in Clinical Studies for Drug Development" (Drug Evaluation Committee, Japan Pharmaceutical Manufacturers Association; April 2018).

13.2 IRB

13.2.1 Review of the Propriety of Conducting the Study

This study will not be initiated without review and approval of the protocol, informed consent form, and appropriateness of conducting the study from the viewpoint of ethical, scientific, and medical appropriateness by the IRB consulted by the director of each investigative site.

13.2.2 Follow-up Review

The investigator will submit a brief summary of the actual status of the study in writing to the director of the investigative site for review at least once a year or upon request from the IRB.

13.3 Selection of Subjects to be Enrolled in the Study and Assurance of Their Safety

In order to protect the human rights of subjects, the investigator or subinvestigator must carefully examine the appropriateness of participating in the study for each subject. For example, individuals who may be put at a disadvantage in the case of refusal to participate (socially vulnerable people) should not be enrolled in the study.

The investigator or subinvestigator will determine whether each subject is eligible for enrollment based on the inclusion and exclusion criteria to ensure that the study will not include any subjects whose safety cannot be ensured.

Throughout the study, the investigator or subinvestigator will keep track of subjects' conditions by ensuring emergency contact or any other method and will collect and share safety information that may be relevant to investigational product. If a AE occurs, the investigator or subinvestigator will ensure the safety of the subject by taking such measures as providing appropriate treatment to the subject and if necessary, discontinuing investigational product.

13.4 Protection of Subjects' Personal Information and Privacy

In filling out the eCRF, the investigator or subinvestigator will identify each subject with his or her subject identification code to ensure that the subject's personal information is properly protected.

Individuals who belong to the units of the Sponsor or the in-country caretaker that are involved in the study must not disclose, without a valid reason, confidential information on a subject to which they have access in the performance of their duties.

13.5 Informed Consent

The investigator or subinvestigator will fully explain the nature of the study to each potential subject (or his or her legally acceptable representative) before their participation in the study in a language understandable for them, based on the Information for Subjects/Informed Consent Form (ICF) provided elsewhere. A legally acceptable representative of a subject <20 years must be a person in parental authority or a guardian of a minor. The subject (or his or her legally acceptable representative) will be given sufficient time to decide whether or not to participate in the study, and the investigator or subinvestigator will obtain written consent (using the ICF developed elsewhere) from the subject (or his or her legally acceptable representative) on a voluntary basis before the screening examinations.

The ICF will be personally signed and dated by the subject and then by the investigator or subinvestigator who has conducted the informed consent discussion.

If the clinical research coordinator gives supplemental explanation, he or she will also sign and date the informed consent form. If the subject is unable to sign because of handwriting difficulties, oral consent will be obtained from the subject and written consent will be obtained from the subject's legally acceptable representative. In such a case, the following will be recorded in informed consent: date of written consent by the subject's legally acceptable representative, his/her relationship to the subject, reason for the subject's legally acceptable representative giving written consent (handwriting difficulties), and date of oral consent by the subject.

13.5.1 Informed Consent (Assent) for Subjects (Pediatric Patients)

Before enrollment in the study, the investigator or subinvestigator will explain a candidate pediatric subject the nature of the study to the extent that he or she can understand, based on the Information for Subjects/ICF (for Assent) developed elsewhere. In addition to this, the clinical research coordinator may also give a supplemental explanation regarding the study. Pediatric patients who have the ability to provide assent will be given sufficient time to consider whether to participate in the study. After that, the investigator or subinvestigator will obtain assent (consent given by a pediatric subject, which is not legally required) for participation in the study from the candidate subject on a voluntary basis before the start of screening.

If oral assent is obtained from the subject, obtainment of oral assent will be recorded on the informed consent form (ICF) signed by the subject's legally acceptable representative.

If written assent is obtained from the subject, the ICF will be personally signed and dated by the investigator or subinvestigator who has conducted the informed consent discussion and by the subject. If the clinical research coordinator gives supplemental explanation, he or she will also sign and date the ICF.

13.5.2 Points to Note regarding Section 13.5 and Section 13.5.1

The investigator or subinvestigator will provide the subject (or the subject's legally acceptable representative) with a copy of the ICF for the subject's records and the Information for Subjects. The investigator or subinvestigator will retain the original ICF for storage at the investigative site according to the policy of each institution.

The Information for Subjects/ICF must include information required by the GCP guidelines and the applicable laws and regulations.

Whenever any new information that may influence the subject's willingness to continue participation in the study becomes available, the investigator or subinvestigator will promptly update the subject to confirm his or her willingness to continue in the study, and enter the details of the explanation given, date of the explanation, name of the person who indicated the subject's decision, and a description of the subject's decision in the medical records.

If the investigator determines that the Information for Subjects/ICF needs to be updated to include the explanation given to subjects, the investigator will promptly revise it and gain the IRB/IEC's approval. Subsequently, the investigator or subinvestigator will conduct the informed consent discussion again using the new Information for Subjects/ICF and obtain written consent to continue in the study from the subjects (or their legally acceptable representative) through the same procedure as for the initial consent If possible, informed assent should also be obtained from the subject in person.

If a subject who was a minor (<20 years) at the time of informed consent (assent) comes of age (20 years) during the study, first-person informed consent must be newly obtained from the subject.

13.5.3 Information for Subjects/Informed Consent Form

The written information provided to subjects and the ICF should include explanation of the following:

1) That the study involves research;
2) Study objectives
3) Name, title, and contact information of the investigator;
4) Study method;
5) Expected beneficial effects of investigational product on the subject's mental and physical health (when there is no such benefit to the subject, the subject should be made aware of this) and expected hazards or inconveniences to the subject;
6) The alternative procedure(s) or course(s) of treatment;
7) The expected duration of the subject's participation in the study;
8) That the subject is allowed to withdraw from the study at any time;
9) That the subject may refuse or withdraw from the study without penalty or loss of benefits to which the subject is otherwise entitled;
10) That the monitors, the auditors, the IRB of the investigative site, and other relevant parties will be granted direct access to the source documents, without violating the confidentiality of the subject;
11) That the subject's identity will remain confidential;
12) Contact information of the person(s) at the investigative site to contact in the event of study-related health injury;
13) That necessary treatment will be provided to the subject in the event of study-related health injury;
14) The compensation available to the subject in the event of study-related injury;

15) The types of the IRBs that will investigate and review the propriety of the study and others, issues to be investigated and reviewed at each IRB, and other matters related to the IRBs involved in the study;
16) The anticipated expenses, if any, to the subject for participating in the study; and
17) Other relevant information related to the study.

Neither of the following should be included in the Information for Subjects/ICF:

1) Words and phrases that expressly or impliedly, make potential subjects waive their rights; and
2) Words and phrases that expressly or impliedly, discharge the Sponsor, investigative site, investigator, or subinvestigator from any liability that they may have, or reduce such liability.

The explanation about the genetic testing (NUDT15 codon 139 polymorphism analysis in this study) should include the following information:

1) Purpose of the testing;
2) Relation of the testing to the study;
3) Subjects targeted;
4) That the NUDT15 codon 139 polymorphism analysis is essential for this study and subjects who do not give consent for the testing cannot participate in the study;
5) Time and method of the NUDT15 codon 139 polymorphism analysis;
6) Time of and procedures for storage and disposal of samples for the NUDT15 codon 139 polymorphism analysis;
7) Measures taken to protect personal information;
8) Benefits, disadvantages, and burdens associated with the subject's giving consent for the testing;
9) Withdrawal of consent:
    - That the subject is allowed to withdraw his or her consent at any time.
    - That the samples collected from the subject will be discarded immediately after consent withdrawal but data obtained before consent withdrawal will not be discarded.
    - That the subject will be withdrawn from the study if he or she withdraws consent for the testing.
10) That the monitors, the auditors, the IRB of the investigative site, and regulatory authorities will be granted direct access to source documents including analysis results;
11) Publication of analysis results; and
12) Rights arising from obtaining the analysis results.

13.6 Audit and Inspection

The Sponsor or in-country caretaker or regulatory authorities can inspect the investigative site according to the ICH E6 Guidelines. The Sponsor or the in-country caretaker will verify, through monitoring and auditing, that the study, data generation, recording, and reporting are being conducted in compliance with the protocol and ICH E6-GCP. The Quality Assurance Unit of the Sponsor or the in-country caretaker, which is independent of the Clinical Development Department, will be responsible for inspecting the study.

The investigator must accept that regulatory authorities may conduct an inspection to verify compliance of the study with GCP.

The management and quality assurance of data will be conducted according to the standard operating procedures (SOPs) for clinical studies and auditing of the Sponsor or the in-country caretaker.

13.7 Expenses Related to the Study

The details of the expenses for all examinations and imaging tests conducted during the study treatment period and the medication or injection of pharmaceutical products with the indication similar to that expected for the test drug will be specified in the clinical study agreement.

13.8 Expenses for Reducing the Burden to Subjects Resulting from Participation in the Study

In order to reduce the burden to subjects resulting from participation in the study, the Sponsor or the in-country caretaker will bear the compensation or reimbursements for incurred expenses to the subjects through the relevant investigative sites, in accordance with the applicable rules of each investigative site.

13.9 Compensation for Health Injury

In the event of any study-related disease or health injury in a subject, appropriate therapeutic measures will be taken in accordance with the clauses on compensation in the Information for Subjects/ICF or the Clinical Trial Agreement. An information leaflet containing essential information about the compensation will be attached to the Information for Subjects/ICF.

Basic Policy on Compensation for Health Injury

1) In the event of any study-related health injury in a subject, the investigator or subinvestigator will take necessary measures, including appropriate treatment.
2) If any study-related health injury occurs to a subject and if any dispute with the subject and others arises or may arise, the investigative site should immediately notify the Sponsor or the in-country caretaker, and the two (or three) parties will cooperate to settle the dispute.
3) If liability for damages arises out of a study-related health injury, the Sponsor will reimburse the investigative site for all of the compensation and settlement expenses incurred by it, unless the investigative site is responsible for the health injury.
4) If compensation liability arises out of a study-related health injury in a subject, the Sponsor will incur the compensation liability. For medical expenses required for treatment, the Sponsor will compensate for the subject's out-of-pocket medical expenses, excluding benefits paid by health insurance or other sources.
5) The compensation liability described above will be incurred according to the compensation rules specified by the Sponsor or the in-country caretaker.

13.10 Publication Policy

The investigator or subinvestigator must obtain prior agreement from the Sponsor before publishing data derived from this study in an academic conference, journal, or other media. The detailed publication policy of the Sponsor is described in the clinical study agreement.

14 PROTOCOL COMPLIANCE, DEVIATIONS OR CHANGES, AND AMENDMENTS

14.1 Compliance with the Protocol

The investigator or subinvestigator will comply with the protocol on which the investigator and the Sponsor or in-country caretaker have agreed and which has been approved in writing by the IRB consulted by the director of the investigative site.

14.2 Deviations from or Changes to the Protocol

The investigator or subinvestigator must not deviate from or make changes to the protocol unless obtaining the prior written agreement of the Sponsor or the in-country caretaker and the written approval of the IRB based on its prior review. In the event of a deviation from or change to the protocol, the investigator or subinvestigator will make a record of all of the relevant actions regardless of the reason.

For medical reasons such as the need to eliminate immediate hazards to the subject, the investigator or subinvestigator may deviate from or make changes to the protocol without the prior written agreement of the Sponsor or the in-country caretaker or the prior written approval of the IRB. In such a case, the investigator should immediately submit a document describing the nature of and reason for the deviation or change to the Sponsor or in-country caretaker and the director of the investigative site. The investigator will also submit the document to the IRB via the director of the investigative site for its approval, and in addition, will obtain the written consent of the director of the investigative site and the written agreement of the Sponsor or the in-country caretaker.

The investigator should submit, as soon as possible, a description of the deviation or change, the reason, and if appropriate, a proposed amendment to the protocol to the Sponsor or in-country caretaker, the director of the investigative site, and the IRB (via the director of the investigative site) for their approval. The written consent of the director of the investigative site and the written agreement of the Sponsor or the in-country caretaker should also be obtained.

14.3 Protocol Amendments

When the Sponsor amends the protocol, the Sponsor or the in-country caretaker will fully inform each investigator using the amended version of the protocol or a written description of the amendment to obtain their agreement. The investigator will conduct the study according to the amended protocol after receiving the written approval of the IRB based on its prior review. However, this does not apply to amendments that only involve administrative issues (e.g., changes in affiliation, job title, address, and telephone number).

15 STUDY COMPLETION

Upon completion of the protocol-specified dosing and observations of all subjects at the investigative site, the investigator will report the study completion and outlined study results to the director of the investigative site in writing.

The director of the investigative site will immediately notify the IRB and the Sponsor or in-country caretaker of study completion in writing and at the same time, report the outlined study results based on the report provided by the investigator.

16 RECORD KEEPING

The investigative site, IRB, and the Sponsor or in-country caretaker will retain records related to the study and subjects' medical records until either of the following dates whichever comes later. Further handling of the records will be discussed between the study director and the Sponsor or in-country caretaker.

- The date of the marketing authorization granted for SHP674 (or, in the case of development discontinuation, the date that is 3 years after the date of decision of development discontinuation or the date of being notified of the discontinuation). However, the Sponsor or the in-country caretaker must retain the records until the date of reexamination completion if the drug requires post-approval reexamination according to the provisions of the Pharmaceuticals and Medical Devices Act and if the period to complete the reexamination is more than 5 years.
- The date that is 3 years after the premature termination of the study.

When further retention of the records becomes impossible, the investigative site must notify the Sponsor or the in-country caretaker and move the relevant records to a mutually agreed place.

The investigator will retain the relevant documents or records related to the study according to the instructions of the director of the investigative site.

16.1 Retention of Source Documents Related to Plasma Asparaginase Activity

Source documents related to plasma asparaginase activity measurement will be retained at the analytical laboratory. The retention period will be until either of the following dates, whichever comes later. Further handling of the documents will be discussed between the study director and the Sponsor or in-country caretaker.

- The date that is 5 years after the date of the marketing authorization granted for SHP674 (or, in the case of development discontinuation, the date that is 3 years after the date of being notified of the discontinuation). In this regard, however, the date of reexamination completion will be applied if the drug requires post-approval reexamination according to the provisions of the Pharmaceuticals and Medical Devices Act and if the period to complete the reexamination is more than 5 years.
- The date that is 3 years after the premature termination of the study.

16.2 Retentions of Source Documents Related to Laboratory and Other Tests

The retention period will be until either of the following dates, whichever comes later. Further handling of the documents will be discussed between the study director and the Sponsor or in-country caretaker.

- The date that is 5 years after the date of the marketing authorization granted for SHP674 (or, in the case of development discontinuation, the date that is 3 years after the date of being notified of the discontinuation). In this regard, however, the date of reexamination completion will be applied if the drug requires post-approval reexamination according to the provisions of the Pharmaceuticals and Medical Devices Act and if the period to complete the reexamination is more than 5 years.
- The date that is 3 years after the premature termination of the study.

16.3 Biological Sample Archiving

Blood samples derived from subjects who provide consent for the storage and use of samples for research will be stored until the time of marketing approval of SHP674, the test drug for this study, in Japan or the time of completion of the final clinical study report for this study, whichever comes later. The samples will then be discarded after being treated appropriately so that they cannot be used by others for other research.

17 STUDY ADMINISTRATIVE STRUCTURE

See Attachment 1 to the protocol (supplement).

18 MAIN RESPONSIBILITIES OF THE INVESTIGATOR

See Attachment 2 to the protocol (supplement).

19 REFRENCES

1. Disease Registry Committee, the Japanese Society of Pediatric Hematology/Oncology. Summarized Data on the Registration of Patients with Hematologic Neoplasms. Available from: https://jspho.jp/old/standing_committee/disease_registry.html
2. Horibe K, Saito AM, Takimoto T, Tsuchida M, Manabe A, Shima M, et al. Incidence and survival rates of hematological malignancies in Japanese children and adolescents (2006–2010): based on registry data from the Japanese Society of Pediatric Hematology. Int J Hematol. 2013 Jul;98(1):74-88.
3. The Japanese Society of Pediatric Hematology/Oncology. Pediatric Hematology and Oncology. Shindan to Chiryo Sha, Inc.
4. Swerdlow SH, et al. eds. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Lyon, IARC; 2008
5. Japanese Society of Hematology. Practical Guidelines for Hematological Malignancies. 2018. Kanehara & Co., Ltd.
6. The Japanese Society of Pediatric Hematology/Oncology. A Practical Guideline for Pediatric Leukemia and Lymphoma. 2016. Kanehara & Co., Ltd.
7. Ortega JA, Nesbit ME Jr., Donaldson MH, Hittle RE, Weiner J, Karon M, et al. L-Asparaginase,vincristine, and prednisone for induction of first remission in acute lymphocytic leukemia. Cancer Res. 1977 Feb;37(2):535-40.
8. Clarke M, Gaynon P, Hann I, Harrison G, Masera G, Peto R, et al. CNS-directed therapy for childhood acute lymphoblastic leukemia: Childhood ALL Collaborative Group overview of 43 randomized trials. J Clin Oncol. 2003 May 1;21 (9):1798-809.
9. Tubergen DG, Gilchrist GS, O'Brien RT, Coccia PF, Sather HN, Waskerwitz MJ, et al. Improved outcome with delayed intensification for children with acute lymphoblastic leukemia and intermediate presenting features: a Childrens Cancer Group phase III trial. J Clin Oncol. 1993 Mar;11(3):527-37.
10. Avramis VI, Sencer S, Periclou AP, Sather H, Bostrom BC, Cohen LJ, et al. A randomized comparison of native Escherichia coli asparaginase and polyethylene glycol conjugated asparaginase for treatment of children with newly diagnosed standard-risk acute lymphoblastic leukemia: a Children's Cancer Group study. Blood. 2002 Mar 15;99(6):1986-94.
11. Rizzari C, Citterio M, Zucchetti M, Conter V, Chiesa R, Colombini A, et al. A pharmacological study on pegylated asparaginase used in front-line treatment of children with acute lymphoblastic leukemia. Haematologica. 2006 Jan;91(1):24-31.
12. Silverman LB, Gelber RD, Dalton VK, Asselin BL, Barr RD, Clavell LA, et al. Improved outcome for children with acute lymphoblastic leukemia: results of Dana-Farber Consortium Protocol 91-01. Blood. 2001 Mar 1;97(5):1211-8.
13. Matloub Y, Bostrom BC, Hunger SP, Stork LC, Angiolillo A, Sather H, et al. Escalating intravenous methotrexate improves event-free survival in children with standard-risk acute lymphoblastic leukemia: a report from the Children's Oncology Group. Blood. 2011 Jul 14;118(2):243-51.

14. Seibel NL, Steinherz PG, Sather HN, Nachman JB, Delaat C, Ettinger LJ, et al. Early postinduction intensification therapy improves survival for children and adolescents with high-risk acute lymphoblastic leukemia: a report from the Children's Oncology Group. Blood. 2008 Mar 1;111(5):2548-55.
15. LeClerc JM, Billett AL, Gelber RD, Dalton V, Tarbell N, Lipton JM, et al. Treatment of childhood acute lymphoblastic leukemia: results of Dana-Farber ALL Consortium Protocol 87-01. J Clin Oncol. 2002 Jan 1;20(1):237-46.
16. Dinndorf PA, Gootenberg J, Cohen MH, Keegan P, Pazdur R. FDA drug approval summary: pegaspargase (oncaspar) for the first-line treatment of children with acute lymphoblastic leukemia (ALL). Oncologist. 2007 Aug;12(8):991-8.
17. Koh K, Kato M, Saito AM, Kada A, Kawasaki H, Okamoto Y, et al. Phase II/III study in children and adolescents with newly diagnosed B-cell precursor acute lymphoblastic leukemia: protocol for a nationwide multicenter trial in Japan. Jpn J Clin Oncol. 2018 Jul 1;48(7):684-91
18. NCCN Guidelines: Acute Lymphoblastic Leukemia, Version 1. 2018.
19. Body Constitution Assessment in Japanese Children [Internet]. The Japanese Society for Pediatric Endocrinology; July 2011 [cited on 9 May, 2017]. Available from: http://jspe.umin.jp/medical/taikaku.html
20. Kakuta Y, Kawai Y, Okamoto D, Takagawa T, Ikeya K, Sakuraba H, et al. NUDT15 codon 139 is the best pharmacogenetic marker for predicting thiopurine-induced severe adverse events in Japanese patients with inflammatory bowel disease: a multicenter study. J Gastroenterol. 2018 Sep;53(9):1065-78.