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

Summary

EudraCT number	2022-002190-28
Trial protocol	Outside EU/EEA
Global end of trial date	04 February 2022

Results information

Result version number	v1 (current)
This version publication date	14 September 2022
First version publication date	14 September 2022

Trial information

Trial identification

Sponsor protocol code	SHP674-201/CL1-95014-001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04067518
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Institut de Recherches Internationales Servier
Sponsor organisation address	50 Rue Carnot, Suresnes, France, 92284
Public contact	Clinical Studies Department, Institut de Recherches Internationales Servier, clinicaltrials@servier.com
Scientific contact	Clinical Studies Department, Institut de Recherches Internationales Servier, clinicaltrials@servier.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	04 February 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	04 February 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Phase 1:
To assess the safety and tolerability of a single dose of SHP674 in Japanese subjects (dose confirmation) in the tolerability assessment period of Part 1.

Phase 2:
To assess the safety, pharmacokinetics and efficacy of SHP674 dose in Part 2 (found to be tolerated in Part 1) in the treatment of newly diagnosed untreated acute lymphoblastic leukemia (ALL) in Japanese subjects.

Protection of trial subjects:

Subjects provided informed assent or written informed consent. For subjects (young children) who provided informed assent when applicable as per their age, a written informed consent was obtained from a legally acceptable representative/parent.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 October 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Japan: 26
Worldwide total number of subjects	26
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	1
Children (2-11 years)	19
Adolescents (12-17 years)	6

Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were enrolled at 8 investigative sites in Japan from 17 October 2019 to 18 January 2021.

Pre-assignment

Screening details:

A total of 28 subjects were enrolled, 3 into Part 1 and 25 into Part 2, of which 26 subjects were treated, 3 in Part 1 and 23 in Part 2.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Part 1: SHP674

Arm description:

Subjects with ALL who were stratified into the standard risk (SR) or intermediate risk (IR) groups received total 3 doses of SHP674, 2500 international units per square metre (IU/m^2) (if body surface area [BSA] ≥0.6 m^2) or 82.5 international units per kilogram (IU/kg) (if BSA <0.6 m^2) intravenously (IV) on Day 12 of Remission induction therapy (SR: IA2/IR: IA4) in the 5-week tolerability assessment period, Day 2 of re-induction therapy (conducted twice) in the 36-week treatment period.

Arm type	Experimental
Investigational medicinal product name	SHP674
Investigational medicinal product code	
Other name	Pegaspargase
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

SHP674 administered by 1 to 2 hours of drip infusion, dose determination: if BSA ≥0.6 m^2: 2500 IU/m^2 every 14 days if BSA <0.6 m^2: 82.5 IU/kg every 14 days.

Arm title	Part 2: SHP674

Arm description:

Subjects with ALL who were stratified into the SR or IR groups received total 3 doses of SHP674, 2500 IU/m^2 (if BSA ≥0.6 m^2) or 82.5 IU/kg (if BSA <0.6 m^2) IV on Day 12 of Remission induction therapy (SR: IA2/IR: IA4), Day 2 of re-induction therapy (conducted twice) in the 41-week treatment period and who were stratified into the HR group received total 8 doses of SHP674, 2500 IU/m^2 (if BSA ≥0.6 m^2) or 82.5 IU/kg (if BSA <0.6 m^2) IV on Day 12 of Remission induction therapy (IA4), Day 38 of early consolidation therapy, Day 6 of consolidation therapies (HR3, HR2), Day 7 of consolidation therapy (HR1), Day 2 of re-induction therapy (conducted thrice) in the 45-week treatment period.

Arm type	Experimental
Investigational medicinal product name	SHP674
Investigational medicinal product code	
Other name	Pegaspargase
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

SHP674 administered by 1 to 2 hours of drip infusion, dose determination: if BSA ≥0.6 m^2: 2500 IU/m^2 every 14 days if BSA <0.6 m^2: 82.5 IU/kg every 14 days.

Number of subjects in period 1	Part 1: SHP674	Part 2: SHP674
Started	3	23
Safety Analysis Set	3	23
Full Analysis Set	0 [1]	23
Immunogenicity Analysis Set	3	22
Pharmacokinetic Analysis Set	3	23
Completed	2	20
Not completed	1	3
Adverse Events	1	3

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Full analysis set (FAS) included all subjects who were enrolled and received SHP674 in Part 2 of the study. Hence this analysis set did not include any subjects in Part 1 arm group.

Baseline characteristics

Reporting groups	
Reporting group title	Part 1: SHP674

Reporting group description:

Subjects with ALL who were stratified into the standard risk (SR) or intermediate risk (IR) groups received total 3 doses of SHP674, 2500 international units per square metre (IU/m^2) (if body surface area [BSA] ≥0.6 m^2) or 82.5 international units per kilogram (IU/kg) (if BSA <0.6 m^2) intravenously (IV) on Day 12 of Remission induction therapy (SR: IA2/IR: IA4) in the 5-week tolerability assessment period, Day 2 of re-induction therapy (conducted twice) in the 36-week treatment period.

Reporting group title	Part 2: SHP674

Reporting group description:

Subjects with ALL who were stratified into the SR or IR groups received total 3 doses of SHP674, 2500 IU/m^2 (if BSA ≥0.6 m^2) or 82.5 IU/kg (if BSA <0.6 m^2) IV on Day 12 of Remission induction therapy (SR: IA2/IR: IA4), Day 2 of re-induction therapy (conducted twice) in the 41-week treatment period and who were stratified into the HR group received total 8 doses of SHP674, 2500 IU/m^2 (if BSA ≥0.6 m^2) or 82.5 IU/kg (if BSA <0.6 m^2) IV on Day 12 of Remission induction therapy (IA4), Day 38 of early consolidation therapy, Day 6 of consolidation therapies (HR3, HR2), Day 7 of consolidation therapy (HR1), Day 2 of re-induction therapy (conducted thrice) in the 45-week treatment period.

Reporting group values	Part 1: SHP674	Part 2: SHP674	Total
Number of subjects	3	23	26
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	10.2	6.7	
standard deviation	± 2.63	± 4.79	-
Gender categorical Units: Subjects			
Female	2	11	13
Male	1	12	13
Race Units: Subjects			
Asian	3	23	26

End points

End points reporting groups

Reporting group title	Part 1: SHP674

Reporting group description:

Subjects with ALL who were stratified into the standard risk (SR) or intermediate risk (IR) groups received total 3 doses of SHP674, 2500 international units per square metre (IU/m^2) (if body surface area [BSA] ≥0.6 m^2) or 82.5 international units per kilogram (IU/kg) (if BSA <0.6 m^2) intravenously (IV) on Day 12 of Remission induction therapy (SR: IA2/IR: IA4) in the 5-week tolerability assessment period, Day 2 of re-induction therapy (conducted twice) in the 36-week treatment period.

Reporting group title	Part 2: SHP674

Reporting group description:

Subjects with ALL who were stratified into the SR or IR groups received total 3 doses of SHP674, 2500 IU/m^2 (if BSA ≥0.6 m^2) or 82.5 IU/kg (if BSA <0.6 m^2) IV on Day 12 of Remission induction therapy (SR: IA2/IR: IA4), Day 2 of re-induction therapy (conducted twice) in the 41-week treatment period and who were stratified into the HR group received total 8 doses of SHP674, 2500 IU/m^2 (if BSA ≥0.6 m^2) or 82.5 IU/kg (if BSA <0.6 m^2) IV on Day 12 of Remission induction therapy (IA4), Day 38 of early consolidation therapy, Day 6 of consolidation therapies (HR3, HR2), Day 7 of consolidation therapy (HR1), Day 2 of re-induction therapy (conducted thrice) in the 45-week treatment period.

Primary: Part 1: Percentage of Subjects With Treatment-Emergent Adverse Events (TEAEs) and SHP-674-Related TEAEs During the Tolerability Assessment Period

End point title	Part 1: Percentage of Subjects With Treatment-Emergent Adverse Events (TEAEs) and SHP-674-Related TEAEs During the Tolerability Assessment Period[1][2]

End point description:

An adverse event (AE) is defined as any untoward medical occurrence in a subject after signing informed consent. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease, whether or not it is related to the investigational product. 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 related adverse event signifies that there is a reasonable causal relationship between study treatment and an AE. Safety Analysis Set (SAF) included all subjects who had received at least one dose of SHP674 in Part 1 or Part 2 of the study.

End point type	Primary

End point timeframe:

Enrollment up to 5 weeks

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was planned or performed for this end point.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: As pre-specified in the protocol, this end point was analysed only for Part 1.

End point values	Part 1: SHP674			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: percentage of subjects				
number (not applicable)				
TEAEs	100.0			
SHP-674-Related TEAEs	100.0			

Statistical analyses

No statistical analyses for this end point

Primary: Part 2: Percentage of Subjects Who Achieved a Plasma Asparaginase Activity of ≥0.1 International Units Per Millilitre (IU/mL) 14 Days (336 Hours) After the First Dose of SHP674

End point title	Part 2: Percentage of Subjects Who Achieved a Plasma Asparaginase Activity of ≥0.1 International Units Per Millilitre (IU/mL) 14 Days (336 Hours) After the First Dose of SHP674[3][4]

End point description:

Full Analysis Set (FAS) included all subjects who were enrolled and received SHP674 in Part 2 of the study.

End point type	Primary

End point timeframe:

14 days after the first dose of SHP674

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was planned or performed for this end point.

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: As pre-specified in the protocol, this end point was analysed only for Part 2.

End point values	Part 2: SHP674			
Subject group type	Reporting group			
Number of subjects analysed	23			
Units: percentage of subjects				
number (confidence interval 95%)	100.0 (85.2 to 100.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Parts 1 and 2: Percentage of Subjects With Treatment-Emergent Adverse Events (TEAEs) and SHP-674-Related TEAEs

End point title	Parts 1 and 2: Percentage of Subjects With Treatment-Emergent Adverse Events (TEAEs) and SHP-674-Related TEAEs

End point description:

An adverse event (AE) is defined as any untoward medical occurrence in a subject after signing informed consent. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease, whether or not it is related to the investigational product. 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 days after the last dose of investigational product, or until the start of a new therapy, whichever occurs first. A related TEAE

signifies that there is a reasonable causal relationship between study treatment and an AE. SAF included all subjects who had received at least one dose of SHP674 in Part 1 or Part 2 of the study.

End point type	Secondary

End point timeframe:

Parts 1 and 2: Up to 30 days after last dose of study drug (approximately 49 weeks)

End point values	Part 1: SHP674	Part 2: SHP674		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	23		
Units: percentage of subjects				
number (not applicable)				
TEAEs	100.0	100.0		
SHP-674-Related TEAEs	100.0	100.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Parts 1 and 2: Percentage of Subjects With Anti-Drug (SHP674) Antibody (ADA) and Anti-Polyethylene Glycol (PEG) Antibody

End point title	Parts 1 and 2: Percentage of Subjects With Anti-Drug (SHP674) Antibody (ADA) and Anti-Polyethylene Glycol (PEG) Antibody

End point description:

Immunogenicity analysis set (IMAS) included all subjects who had received at least one dose of SHP674 in Part 1 or Part 2 of the study and had at least one evaluable post-dose sample. If the pre-dose sample was missing it was considered negative.

End point type	Secondary

End point timeframe:

Part 1: Predose and 25 days post dose; Part 2: Predose and 25 days post dose

End point values	Part 1: SHP674	Part 2: SHP674		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	22		
Units: percentage of subjects				
number (not applicable)				
ADA: Pre-dose	0	18.2		
ADA: 25 Days Post Dose	0	4.5		
Anti-PEG Antibody: Pre-dose	0	9.1		
Anti-PEG Antibody: 25 Days Post Dose	0	4.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Part 1: Percentage of Subjects Who Achieved a Plasma Asparaginase Activity of ≥0.1 IU/mL 14 Days (336 Hours) After the First Dose of SHP674

End point title	Part 1: Percentage of Subjects Who Achieved a Plasma Asparaginase Activity of ≥0.1 IU/mL 14 Days (336 Hours) After the First Dose of SHP674[5]

End point description:

SAF included all subjects who had received at least one dose of SHP674 in Part 1 or Part 2 of the study.

End point type	Secondary

End point timeframe:

14 days after the first dose of SHP674

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: As pre-specified in the protocol, this end point was analysed only for Part 1.

End point values	Part 1: SHP674			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: percentage of subjects				
number (confidence interval 95%)	100.0 (29.2 to 100.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Percentage of Subjects With Plasma Asparaginase Activity of ≥0.1 IU/mL or <0.1 IU/mL

End point title	Part 2: Percentage of Subjects With Plasma Asparaginase Activity of ≥0.1 IU/mL or <0.1 IU/mL[6]

End point description:

FAS included all subjects who were enrolled and received SHP674 in Part 2 of the study. 'Number analysed (n)' indicates the number of subjects analysed at the specified timepoint.

End point type	Secondary

End point timeframe:

Day 1 (pre-dose, 5 min, 4 hours, 24 hours post dose), Days 2, 4, 11, 14, 18, 25 post dose

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: As pre-specified in the protocol, this end point was analysed only for Part 2.

End point values	Part 2: SHP674			
Subject group type	Reporting group			
Number of subjects analysed	23			
Units: percentage of subjects				
number (confidence interval 95%)				
≥0.1 IU/mL: Day 1 (pre-dose)	0.0 (0.0 to 14.8)			

≥0.1 IU/mL: Day 1 (5 mins post dose) (n=22)	100.0 (84.6 to 100.0)			
≥0.1 IU/mL: Day 1 (4 hours post dose)	100.0 (85.2 to 100.0)			
≥0.1 IU/mL: Day 1 (24 hours post dose)	100.0 (85.2 to 100.0)			
≥0.1 IU/mL: Day 2 post dose	100.0 (85.2 to 100.0)			
≥0.1 IU/mL: Day 4 post dose	100.0 (85.2 to 100.0)			
≥0.1 IU/mL: Day 11 post dose	100.0 (85.2 to 100.0)			
≥0.1 IU/mL: Day 14 post dose	100.0 (85.2 to 100.0)			
≥0.1 IU/mL: Day 18 post dose (n=22)	95.5 (77.2 to 99.9)			
≥0.1 IU/mL: Day 25 post dose (n=22)	50.0 (28.2 to 71.8)			
<0.1 IU/mL : Day 1 (pre-dose)	100.0 (85.2 to 100.0)			
<0.1 IU/mL: Day 1 (5 mins post dose) (n=22)	0.0 (0.0 to 15.4)			
<0.1 IU/mL: Day 1 (4 hours post dose)	0.0 (0.0 to 14.8)			
<0.1 IU/mL: Day 1 (24 hours post dose)	0.0 (0.0 to 14.8)			
<0.1 IU/mL: Day 2 post dose	0.0 (0.0 to 14.8)			
<0.1 IU/mL: Day 4 post dose	0.0 (0.0 to 14.8)			
<0.1 IU/mL: Day 11 post dose	0.0 (0.0 to 14.8)			
<0.1 IU/mL: Day 14 post dose	0.0 (0.0 to 14.8)			
<0.1 IU/mL: Day 18 post dose (n=22)	4.5 (0.1 to 22.8)			
<0.1 IU/mL: Day 25 post dose (n=22)	50.0 (28.2 to 71.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Parts 1 and 2: Survival Rate at 1 Year After the Start of Study Treatment

End point title	Parts 1 and 2: Survival Rate at 1 Year After the Start of Study Treatment

End point description:

Survival rate is defined as the percentage of subjects who survived at 1 year after the start of study treatment. SAF included all subjects who had received at least one dose of SHP674 in Part 1 or Part 2 of the study.

End point type	Secondary

End point timeframe:

1 year after the start of study treatment (from first dose up to 12 months)

End point values	Part 1: SHP674	Part 2: SHP674		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	23		
Units: percentage of subjects				
number (not applicable)	100.0	100.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Parts 1 and 2: Event-free Survival Rate at 1 Year After the Start of Study Treatment

End point title	Parts 1 and 2: Event-free Survival Rate at 1 Year After the Start of Study Treatment

End point description:

Event-free survival rate is defined as percentage of subjects who did not experience any event and survived at 1 year after the start of study treatment. SAF included all subjects who had received at least one dose of SHP674 in Part 1 or Part 2 of the study.

End point type	Secondary

End point timeframe:

1 year after the start of study treatment (from first dose up to 12 months)

End point values	Part 1: SHP674	Part 2: SHP674		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	23		
Units: percentage of subjects				
number (not applicable)	100.0	100.0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Parts 1 and 2: Up to 30 days after last dose of study drug (approximately 49 weeks)

Adverse event reporting additional description:

SAF included all subjects who had received at least one dose of SHP674 in Part 1 or Part 2 of the study. As planned and pre-specified in protocol, the safety data was analysed for Part 1 and Part 2 of study.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	Part 1: SHP674

Reporting group description:

Subjects with ALL who were stratified into the SR or IR groups received total 3 doses of SHP674, 2500 international units per square metre (IU/m^2) (if BSA ≥0.6 m^2) or 82.5 IU/kg (if BSA <0.6 m^2) IV on Day 12 of Remission induction therapy (SR: IA2/IR: IA4) in the 5-week tolerability assessment period, Day 2 of re-induction therapy (conducted twice) in the 36-week treatment period.

Reporting group title	Part 2: SHP674

Reporting group description:

Subjects with ALL who were stratified into the SR or IR groups received total 3 doses of SHP674, 2500 IU/m^2 (if BSA ≥0.6 m^2) or 82.5 IU/kg (if BSA <0.6 m^2) IV on Day 12 of Remission induction therapy (SR: IA2/IR: IA4), Day 2 of re-induction therapy (conducted twice) in the 41-week treatment period and who were stratified into the HR group received total 8 doses of SHP674, 2500 IU/m^2 (if BSA ≥0.6 m^2) or 82.5 IU/kg (if BSA <0.6 m^2) IV on Day 12 of Remission induction therapy (IA4), Day 38 of early consolidation therapy, Day 6 of consolidation therapies (HR3, HR2), Day 7 of consolidation therapy (HR1), Day 2 of re-induction therapy (conducted thrice) in the 45-week treatment period.

Serious adverse events	Part 1: SHP674	Part 2: SHP674	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 3 (33.33%)	10 / 23 (43.48%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Platelet count decreased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Anaphylactic transfusion reaction			

subjects affected / exposed	1 / 3 (33.33%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Posterior reversible encephalopathy syndrome			
subjects affected / exposed	0 / 3 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Haemophagocytic lymphohistiocytosis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Pancreatitis acute			
subjects affected / exposed	0 / 3 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 3 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cellulitis			

subjects affected / exposed	0 / 3 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 3 (33.33%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Part 1: SHP674	Part 2: SHP674	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	23 / 23 (100.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 3 (0.00%)	7 / 23 (30.43%)	
occurrences (all)	0	11	
Flushing			

subjects affected / exposed	1 / 3 (33.33%)	3 / 23 (13.04%)	
occurrences (all)	1	3	
General disorders and administration site conditions			
Catheter site pain			
subjects affected / exposed	1 / 3 (33.33%)	3 / 23 (13.04%)	
occurrences (all)	1	3	
Non-cardiac chest pain			
subjects affected / exposed	0 / 3 (0.00%)	2 / 23 (8.70%)	
occurrences (all)	0	2	
Pyrexia			
subjects affected / exposed	0 / 3 (0.00%)	12 / 23 (52.17%)	
occurrences (all)	0	14	
Malaise			
subjects affected / exposed	0 / 3 (0.00%)	4 / 23 (17.39%)	
occurrences (all)	0	4	
Catheter site erythema			
subjects affected / exposed	2 / 3 (66.67%)	1 / 23 (4.35%)	
occurrences (all)	3	1	
Hunger			
subjects affected / exposed	0 / 3 (0.00%)	2 / 23 (8.70%)	
occurrences (all)	0	2	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 3 (33.33%)	1 / 23 (4.35%)	
occurrences (all)	2	1	
Hypogammaglobulinaemia			
subjects affected / exposed	0 / 3 (0.00%)	7 / 23 (30.43%)	
occurrences (all)	0	9	
Seasonal allergy			
subjects affected / exposed	0 / 3 (0.00%)	2 / 23 (8.70%)	
occurrences (all)	0	2	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 3 (33.33%)	1 / 23 (4.35%)	
occurrences (all)	2	2	
Epistaxis			

subjects affected / exposed	0 / 3 (0.00%)	3 / 23 (13.04%)	
occurrences (all)	0	6	
Hypoxia			
subjects affected / exposed	0 / 3 (0.00%)	2 / 23 (8.70%)	
occurrences (all)	0	2	
Upper respiratory tract inflammation			
subjects affected / exposed	0 / 3 (0.00%)	2 / 23 (8.70%)	
occurrences (all)	0	3	
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 3 (0.00%)	2 / 23 (8.70%)	
occurrences (all)	0	2	
Insomnia			
subjects affected / exposed	0 / 3 (0.00%)	6 / 23 (26.09%)	
occurrences (all)	0	10	
Discouragement			
subjects affected / exposed	0 / 3 (0.00%)	4 / 23 (17.39%)	
occurrences (all)	0	8	
Depressive symptom			
subjects affected / exposed	0 / 3 (0.00%)	3 / 23 (13.04%)	
occurrences (all)	0	5	
Substance-induced psychotic disorder			
subjects affected / exposed	0 / 3 (0.00%)	3 / 23 (13.04%)	
occurrences (all)	0	3	
Depressed mood			
subjects affected / exposed	1 / 3 (33.33%)	1 / 23 (4.35%)	
occurrences (all)	2	1	
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	1 / 3 (33.33%)	5 / 23 (21.74%)	
occurrences (all)	2	10	
Alanine aminotransferase increased			
subjects affected / exposed	0 / 3 (0.00%)	13 / 23 (56.52%)	
occurrences (all)	0	32	
Antithrombin III decreased			

subjects affected / exposed	3 / 3 (100.00%)	12 / 23 (52.17%)	
occurrences (all)	9	32	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 3 (0.00%)	13 / 23 (56.52%)	
occurrences (all)	0	34	
Blood albumin decreased			
subjects affected / exposed	2 / 3 (66.67%)	1 / 23 (4.35%)	
occurrences (all)	3	3	
Blood bilirubin increased			
subjects affected / exposed	3 / 3 (100.00%)	9 / 23 (39.13%)	
occurrences (all)	4	13	
Blood cholesterol increased			
subjects affected / exposed	1 / 3 (33.33%)	3 / 23 (13.04%)	
occurrences (all)	1	6	
Blood fibrinogen decreased			
subjects affected / exposed	3 / 3 (100.00%)	16 / 23 (69.57%)	
occurrences (all)	7	42	
Blood lactate dehydrogenase increased			
subjects affected / exposed	2 / 3 (66.67%)	2 / 23 (8.70%)	
occurrences (all)	4	4	
Blood urea increased			
subjects affected / exposed	1 / 3 (33.33%)	2 / 23 (8.70%)	
occurrences (all)	1	2	
Coagulation test abnormal			
subjects affected / exposed	0 / 3 (0.00%)	2 / 23 (8.70%)	
occurrences (all)	0	6	
Fibrin D dimer increased			
subjects affected / exposed	2 / 3 (66.67%)	1 / 23 (4.35%)	
occurrences (all)	2	1	
Fibrin degradation products increased			
subjects affected / exposed	3 / 3 (100.00%)	0 / 23 (0.00%)	
occurrences (all)	3	0	
Gamma-glutamyltransferase increased			

subjects affected / exposed	0 / 3 (0.00%)	9 / 23 (39.13%)	
occurrences (all)	0	12	
Liver function test abnormal			
subjects affected / exposed	2 / 3 (66.67%)	1 / 23 (4.35%)	
occurrences (all)	3	1	
Lymphocyte count decreased			
subjects affected / exposed	0 / 3 (0.00%)	6 / 23 (26.09%)	
occurrences (all)	0	14	
Neutrophil count decreased			
subjects affected / exposed	0 / 3 (0.00%)	7 / 23 (30.43%)	
occurrences (all)	0	39	
Plasmin inhibitor decreased			
subjects affected / exposed	3 / 3 (100.00%)	3 / 23 (13.04%)	
occurrences (all)	7	6	
Plasminogen decreased			
subjects affected / exposed	3 / 3 (100.00%)	3 / 23 (13.04%)	
occurrences (all)	7	7	
Platelet count decreased			
subjects affected / exposed	3 / 3 (100.00%)	22 / 23 (95.65%)	
occurrences (all)	10	67	
Protein total decreased			
subjects affected / exposed	2 / 3 (66.67%)	1 / 23 (4.35%)	
occurrences (all)	3	1	
Weight decreased			
subjects affected / exposed	0 / 3 (0.00%)	2 / 23 (8.70%)	
occurrences (all)	0	3	
White blood cell count decreased			
subjects affected / exposed	3 / 3 (100.00%)	21 / 23 (91.30%)	
occurrences (all)	4	58	
Immunoglobulins decreased			
subjects affected / exposed	0 / 3 (0.00%)	4 / 23 (17.39%)	
occurrences (all)	0	5	
Weight increased			
subjects affected / exposed	0 / 3 (0.00%)	4 / 23 (17.39%)	
occurrences (all)	0	5	
Amylase increased			

subjects affected / exposed	0 / 3 (0.00%)	3 / 23 (13.04%)	
occurrences (all)	0	3	
Blood fibrinogen increased			
subjects affected / exposed	1 / 3 (33.33%)	1 / 23 (4.35%)	
occurrences (all)	1	1	
C-reactive protein increased			
subjects affected / exposed	0 / 3 (0.00%)	2 / 23 (8.70%)	
occurrences (all)	0	3	
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	1 / 3 (33.33%)	4 / 23 (17.39%)	
occurrences (all)	5	5	
Contusion			
subjects affected / exposed	0 / 3 (0.00%)	5 / 23 (21.74%)	
occurrences (all)	0	10	
Fall			
subjects affected / exposed	1 / 3 (33.33%)	2 / 23 (8.70%)	
occurrences (all)	1	2	
Allergic transfusion reaction			
subjects affected / exposed	0 / 3 (0.00%)	2 / 23 (8.70%)	
occurrences (all)	0	2	
Procedural headache			
subjects affected / exposed	0 / 3 (0.00%)	2 / 23 (8.70%)	
occurrences (all)	0	2	
Nervous system disorders			
Cholinergic syndrome			
subjects affected / exposed	2 / 3 (66.67%)	0 / 23 (0.00%)	
occurrences (all)	3	0	
Dizziness			
subjects affected / exposed	2 / 3 (66.67%)	0 / 23 (0.00%)	
occurrences (all)	2	0	
Headache			
subjects affected / exposed	2 / 3 (66.67%)	11 / 23 (47.83%)	
occurrences (all)	4	20	
Leukoencephalopathy			

subjects affected / exposed	0 / 3 (0.00%)	2 / 23 (8.70%)	
occurrences (all)	0	2	
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 3 (0.00%)	2 / 23 (8.70%)	
occurrences (all)	0	2	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 3 (100.00%)	21 / 23 (91.30%)	
occurrences (all)	5	40	
Coagulopathy			
subjects affected / exposed	0 / 3 (0.00%)	5 / 23 (21.74%)	
occurrences (all)	0	5	
Febrile neutropenia			
subjects affected / exposed	2 / 3 (66.67%)	18 / 23 (78.26%)	
occurrences (all)	3	36	
Hypoglobulinaemia			
subjects affected / exposed	1 / 3 (33.33%)	4 / 23 (17.39%)	
occurrences (all)	1	4	
Eye disorders			
Glaucoma			
subjects affected / exposed	0 / 3 (0.00%)	2 / 23 (8.70%)	
occurrences (all)	0	4	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 3 (100.00%)	6 / 23 (26.09%)	
occurrences (all)	6	7	
Constipation			
subjects affected / exposed	2 / 3 (66.67%)	17 / 23 (73.91%)	
occurrences (all)	4	24	
Diarrhoea			
subjects affected / exposed	0 / 3 (0.00%)	10 / 23 (43.48%)	
occurrences (all)	0	17	
Lip dry			
subjects affected / exposed	0 / 3 (0.00%)	4 / 23 (17.39%)	
occurrences (all)	0	4	
Nausea			

subjects affected / exposed	1 / 3 (33.33%)	14 / 23 (60.87%)	
occurrences (all)	2	36	
Proctitis			
subjects affected / exposed	0 / 3 (0.00%)	4 / 23 (17.39%)	
occurrences (all)	0	7	
Stomatitis			
subjects affected / exposed	2 / 3 (66.67%)	13 / 23 (56.52%)	
occurrences (all)	4	24	
Vomiting			
subjects affected / exposed	2 / 3 (66.67%)	19 / 23 (82.61%)	
occurrences (all)	7	123	
Cheilitis			
subjects affected / exposed	0 / 3 (0.00%)	3 / 23 (13.04%)	
occurrences (all)	0	3	
Dental caries			
subjects affected / exposed	0 / 3 (0.00%)	3 / 23 (13.04%)	
occurrences (all)	0	3	
Proctalgia			
subjects affected / exposed	1 / 3 (33.33%)	2 / 23 (8.70%)	
occurrences (all)	1	2	
Abdominal pain upper			
subjects affected / exposed	0 / 3 (0.00%)	2 / 23 (8.70%)	
occurrences (all)	0	2	
Anal erosion			
subjects affected / exposed	0 / 3 (0.00%)	2 / 23 (8.70%)	
occurrences (all)	0	4	
Gastrointestinal disorder			
subjects affected / exposed	1 / 3 (33.33%)	1 / 23 (4.35%)	
occurrences (all)	2	2	
Hepatobiliary disorders			
Hepatic function abnormal			
subjects affected / exposed	1 / 3 (33.33%)	9 / 23 (39.13%)	
occurrences (all)	3	27	
Hepatic steatosis			
subjects affected / exposed	1 / 3 (33.33%)	2 / 23 (8.70%)	
occurrences (all)	1	2	

Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	3 / 3 (100.00%)	17 / 23 (73.91%)	
occurrences (all)	3	17	
Dry skin			
subjects affected / exposed	3 / 3 (100.00%)	10 / 23 (43.48%)	
occurrences (all)	4	13	
Eczema			
subjects affected / exposed	1 / 3 (33.33%)	3 / 23 (13.04%)	
occurrences (all)	2	3	
Erythema			
subjects affected / exposed	1 / 3 (33.33%)	4 / 23 (17.39%)	
occurrences (all)	1	4	
Rash			
subjects affected / exposed	1 / 3 (33.33%)	2 / 23 (8.70%)	
occurrences (all)	2	4	
Dermatitis acneiform			
subjects affected / exposed	0 / 3 (0.00%)	2 / 23 (8.70%)	
occurrences (all)	0	2	
Dermatitis contact			
subjects affected / exposed	0 / 3 (0.00%)	2 / 23 (8.70%)	
occurrences (all)	0	2	
Eczema asteatotic			
subjects affected / exposed	0 / 3 (0.00%)	2 / 23 (8.70%)	
occurrences (all)	0	3	
Ingrowing nail			
subjects affected / exposed	1 / 3 (33.33%)	1 / 23 (4.35%)	
occurrences (all)	1	2	
Miliaria			
subjects affected / exposed	0 / 3 (0.00%)	2 / 23 (8.70%)	
occurrences (all)	0	2	
Pruritus			
subjects affected / exposed	0 / 3 (0.00%)	2 / 23 (8.70%)	
occurrences (all)	0	3	
Renal and urinary disorders			

Calculus urinary			
subjects affected / exposed	1 / 3 (33.33%)	1 / 23 (4.35%)	
occurrences (all)	1	1	
Glycosuria			
subjects affected / exposed	0 / 3 (0.00%)	2 / 23 (8.70%)	
occurrences (all)	0	2	
Endocrine disorders			
Cushingoid			
subjects affected / exposed	1 / 3 (33.33%)	5 / 23 (21.74%)	
occurrences (all)	1	10	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 3 (0.00%)	4 / 23 (17.39%)	
occurrences (all)	0	4	
Pain in extremity			
subjects affected / exposed	0 / 3 (0.00%)	3 / 23 (13.04%)	
occurrences (all)	0	3	
Arthralgia			
subjects affected / exposed	1 / 3 (33.33%)	1 / 23 (4.35%)	
occurrences (all)	1	2	
Muscular weakness			
subjects affected / exposed	0 / 3 (0.00%)	2 / 23 (8.70%)	
occurrences (all)	0	2	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 3 (0.00%)	10 / 23 (43.48%)	
occurrences (all)	0	13	
Bacteraemia			
subjects affected / exposed	1 / 3 (33.33%)	4 / 23 (17.39%)	
occurrences (all)	1	4	
Device related infection			
subjects affected / exposed	0 / 3 (0.00%)	3 / 23 (13.04%)	
occurrences (all)	0	3	
Upper respiratory tract infection			
subjects affected / exposed	0 / 3 (0.00%)	2 / 23 (8.70%)	
occurrences (all)	0	3	

Metabolism and nutrition disorders			
Dyslipidaemia			
subjects affected / exposed	0 / 3 (0.00%)	2 / 23 (8.70%)	
occurrences (all)	0	2	
Hyperglycaemia			
subjects affected / exposed	0 / 3 (0.00%)	5 / 23 (21.74%)	
occurrences (all)	0	5	
Hyperlipidaemia			
subjects affected / exposed	3 / 3 (100.00%)	2 / 23 (8.70%)	
occurrences (all)	5	3	
Hypertriglyceridaemia			
subjects affected / exposed	0 / 3 (0.00%)	10 / 23 (43.48%)	
occurrences (all)	0	21	
Hypoalbuminaemia			
subjects affected / exposed	0 / 3 (0.00%)	4 / 23 (17.39%)	
occurrences (all)	0	6	
Hypoglycaemia			
subjects affected / exposed	0 / 3 (0.00%)	5 / 23 (21.74%)	
occurrences (all)	0	10	
Hypokalaemia			
subjects affected / exposed	0 / 3 (0.00%)	3 / 23 (13.04%)	
occurrences (all)	0	3	
Hyponatraemia			
subjects affected / exposed	0 / 3 (0.00%)	7 / 23 (30.43%)	
occurrences (all)	0	11	
Hypoproteinaemia			
subjects affected / exposed	2 / 3 (66.67%)	8 / 23 (34.78%)	
occurrences (all)	4	21	
Increased appetite			
subjects affected / exposed	1 / 3 (33.33%)	1 / 23 (4.35%)	
occurrences (all)	1	2	
Decreased appetite			
subjects affected / exposed	1 / 3 (33.33%)	5 / 23 (21.74%)	
occurrences (all)	1	7	
Central obesity			

subjects affected / exposed	1 / 3 (33.33%)	1 / 23 (4.35%)	
occurrences (all)	1	2	
Hypercholesterolaemia			
subjects affected / exposed	1 / 3 (33.33%)	1 / 23 (4.35%)	
occurrences (all)	1	2	
Hypophosphataemia			
subjects affected / exposed	0 / 3 (0.00%)	2 / 23 (8.70%)	
occurrences (all)	0	2	
Malnutrition			
subjects affected / exposed	0 / 3 (0.00%)	2 / 23 (8.70%)	
occurrences (all)	0	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 April 2019	-The exclusion criteria, definition of intolerable toxicity and informed consent was modified according to the instruction by PMDA. -The description of the planned study period, withdrawal from the study, backbone therapy drugs provided by the sponsor for investigational use, formulation package presentation, points to note and criteria for changes in treatment during the pre treatment Phase and decision to move to part 2 were adjusted.
20 May 2019	-Added genetic testing to hematological laboratory parameters. -Updates to foreign product used for backbone therapy. -Description of labeling of drug formulation, treatment schedule for study arms, safety parameters and informed consent form was adjusted. - Added genetic testing to the administration details and study procedures. -Added increased blood sampling volume associated with adding the genetic testing.
11 October 2019	-Updated study design, timepoints for investigational product administration, observations, and tests to clarify the definition of Day 1 of consolidation therapy for HR. -The description of nonclinical study results was adjusted and corrected. -The description was adjusted for subject withdrawal, treatment discontinuation, criteria for starting re-induction therapy, definition of intolerable toxicity, screening test items, pregnancy test, definition of adverse events, assessment items, assessment of causal relationship with study treatment, emergency safety measures, safety parameters, handling of missing, unused, and abnormal data and immunogenicity analysis set. -Added dose per package of the drug formulation. -Changes to the descriptions of labeling and storage condition of the formulation. - Corrected dispensing, storage, management, and return of investigational product details. -Specified the backbone therapy drugs that were provided as investigational products and adjusted their description. -Added points to note regarding the number of significant figures calculated for the doses of backbone therapy drugs. -Changes to the criteria for changes in treatment with 6-MP and the points to note. -Added points to note and criteria for changes in treatment during interim maintenance therapy (IM). -Added a description about HBV DNA testing and description adjustment. -Added a description about allowances and description adjustment in ECG measurement schedule. -Corrected immunogenicity description.
22 July 2020	-Clarified the definition of day in drug administration details, study design. -Adjusted description of treatment and dosing schedule, doses of backbone therapy, tolerability assessment, response definition, bone marrow examination, CR evaluation to clarify operations. -Adjusted description of criteria for changes in treatment with each backbone therapy drug, schedule for study procedures, handling of missing, unused and abnormal data and immunogenicity analysis set. -Added new criteria for changes in treatment by symptom. -Added new points to note and criteria for changes in treatment during early consolidation therapy.
22 January 2021	-Corrected criteria for changes in treatment by symptom. -Changed the description of viral test.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported