



Clinical trial results:

A multicentre, Phase II Randomized study, Open-label, with 2-arm Parallel Group, comparing the pharmacokinetics of the Liquid and the Lyophilized Formulations of pegaspargase (S95014) in Treatment of Paediatric Patients with Newly Diagnosed Acute Lymphoblastic Leukemia (ALL)

Summary

EudraCT number	2020-004894-29
Trial protocol	Outside EU/EEA
Global end of trial date	20 May 2022

Results information

Result version number	v1 (current)
This version publication date	15 December 2022
First version publication date	15 December 2022

Trial information

Trial identification

Sponsor protocol code	CL2-95014-002
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04954326
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	Therapeutic Area in Oncology, Institut de Recherches Internationales Servier, +33 155724366, clinicaltrials@servier.com
Scientific contact	Therapeutic Area in Oncology, Institut de Recherches Internationales Servier, +33 155724366, 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	20 May 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 May 2022
Global end of trial reached?	Yes
Global end of trial date	20 May 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to compare the pharmacokinetics (PK) of both lyophilized and liquid S95014 formulations during the induction phase after a single intravenous (IV) dose in newly diagnosed pediatric patients with acute lymphoblastic leukemia (ALL).

Protection of trial subjects:

This study was conducted in accordance with Good Clinical Practice standards, ethical principles stated in the Declaration of Helsinki and applicable regulatory requirements. After the subject has ended his/her participation in the trial, the investigator provided appropriate medication and/or arranged access to appropriate care for the patient.

Background therapy:

Patients received backbone chemotherapy agents as per ALL-MB 2015 protocol and according to local practice

Evidence for comparator: -

Actual start date of recruitment	06 May 2021
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	Russian Federation: 89
Worldwide total number of subjects	89
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)	2
Children (2-11 years)	76
Adolescents (12-17 years)	11
Adults (18-64 years)	0

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The patients were male or female patients aged ≥ 1 to < 18 years, with cytologically confirmed and documented newly diagnosed ALL according to NCCN guidelines 2020, excluding B-cell Burkitt ALL, and with Eastern Cooperative Oncology Group performance status (ECOG PS) 0-2. They were recruited in 7 sites, all located in Russia.

Pre-assignment

Screening details:

93 patients were screened, 89 patients included and assigned to one of the treatment groups: 44 patients in the lyophilized group and 45 in the liquid group. One patient was wrongly included and withdrawn w/o IMP; one patient was assigned to lyo but received liquid formulation. Only the 88 treated patients are described here (as IMP received)

Pre-assignment period milestones

Number of subjects started	89
Number of subjects completed	88

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Protocol deviation: 1
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Period 1

Period 1 title	Induction Phase (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Subjects were randomized to the liquid and lyophilized formulations according to a 1:1 ratio. The randomization was not adaptive. No stratification factor were used during randomization.

Arms

Are arms mutually exclusive?	Yes
Arm title	S95014 Lyophilizate

Arm description:

The included patients were randomized to one of the two treatment groups : the lyophilized S95014 (test drug) or the liquid S95014 (reference drug). The treatment period started on Day 3 of the induction phase until the withdrawal/end-of-study visit and was by IV infusion at the dose of 2500 U/m² over 1-hour.

The patients in this arm received the lyophilized S95014 formulation.

Patient demographics were analysed in the Safety Analysis Set (ie subjects having an administration of S95014).

Arm type	Experimental
Investigational medicinal product name	S95014
Investigational medicinal product code	
Other name	pegaspargase
Pharmaceutical forms	Powder for infusion
Routes of administration	Intravenous use

Dosage and administration details:

S95014 lyophilized powder was reconstituted with 5.2 mL of sterile water for injection.

S95014 was administered IV at the dose of 2500 U/m² on Day 3 of the induction phase, over 1-hour infusion. S95014 dosage was calculated according to body surface area (BSA). The BSA was calculated by the IRS based on the height and weight measured on the day of randomization (D000) and had to be recalculated by the investigator manually on the day of S95014 infusion (D003) (all BSA calculations were rounded to 2 decimal places). $BSA (m^2) = \sqrt{(Height [cm] \times Weight [kg])/3600}$.

Arm title	S95014 Liquid
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Arm description:

The included patients were randomized to one of the two treatment groups : the lyophilized S95014 (test drug) or the liquid S95014 (reference drug). The treatment period started on Day 3 of the induction phase until the withdrawal/end-of-study visit and was by IV infusion at the dose of 2500 U/m² over 1-hour.

The patients in this arm received the liquid S95014 formulation.

Patient demographics were analysed in the Safety Analysis Set (ie subjects having an administration of S95014).

Arm type	Active comparator
Investigational medicinal product name	S95014
Investigational medicinal product code	
Other name	pegaspargase
Pharmaceutical forms	Solution for injection in vial
Routes of administration	Intravenous use

Dosage and administration details:

Each vial contained 750 U S95014 active ingredient per mL.

S95014 was administered IV at the dose of 2500 U/m² on Day 3 of the induction phase, over 1-hour infusion. S95014 dosage was calculated according to body surface area (BSA). The BSA was calculated by the IRS based on the height and weight measured on the day of randomization (D000) and had to be recalculated by the investigator manually on the day of S95014 infusion (D003) (all BSA calculations were rounded to 2 decimal places). $BSA (m^2) = \sqrt{(Height [cm] \times Weight [kg])/3600}$.

Number of subjects in period 1^[1]	S95014 Lyophilizate	S95014 Liquid
Started	43	45
Completed	43	42
Not completed	0	3
Adverse event, serious fatal	-	2
Physician decision	-	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: One patient was wrongly included and withdrawn without IMP administration.

Baseline characteristics

Reporting groups

Reporting group title	S95014 Lyophilizate
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Reporting group description:

The included patients were randomized to one of the two treatment groups : the lyophilized S95014 (test drug) or the liquid S95014 (reference drug). The treatment period started on Day 3 of the induction phase until the withdrawal/end-of-study visit and was by IV infusion at the dose of 2500 U/m² over 1-hour.

The patients in this arm received the lyophilized S95014 formulation.

Patient demographics were analysed in the Safety Analysis Set (ie subjects having an administration of S95014).

Reporting group title	S95014 Liquid
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Reporting group description:

The included patients were randomized to one of the two treatment groups : the lyophilized S95014 (test drug) or the liquid S95014 (reference drug). The treatment period started on Day 3 of the induction phase until the withdrawal/end-of-study visit and was by IV infusion at the dose of 2500 U/m² over 1-hour.

The patients in this arm received the liquid S95014 formulation.

Patient demographics were analysed in the Safety Analysis Set (ie subjects having an administration of S95014).

Reporting group values	S95014 Lyophilizate	S95014 Liquid	Total
Number of subjects	43	45	88
Age categorical			
Units: Subjects			
<10 years	30	38	68
[10,15] years	11	7	18
≥ 16 years	2	0	2
Age continuous			
Units: years			
arithmetic mean	6.9	5.4	
standard deviation	± 4.28	± 3.52	-
Gender categorical			
Units: Subjects			
Female	17	25	42
Male	26	20	46

End points

End points reporting groups

Reporting group title	S95014 Lyophilizate
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Reporting group description:

The included patients were randomized to one of the two treatment groups : the lyophilized S95014 (test drug) or the liquid S95014 (reference drug). The treatment period started on Day 3 of the induction phase until the withdrawal/end-of-study visit and was by IV infusion at the dose of 2500 U/m² over 1-hour.

The patients in this arm received the lyophilized S95014 formulation.

Patient demographics were analysed in the Safety Analysis Set (ie subjects having an administration of S95014).

Reporting group title	S95014 Liquid
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Reporting group description:

The included patients were randomized to one of the two treatment groups : the lyophilized S95014 (test drug) or the liquid S95014 (reference drug). The treatment period started on Day 3 of the induction phase until the withdrawal/end-of-study visit and was by IV infusion at the dose of 2500 U/m² over 1-hour.

The patients in this arm received the liquid S95014 formulation.

Patient demographics were analysed in the Safety Analysis Set (ie subjects having an administration of S95014).

Subject analysis set title	Pharmacokinetic Analysis Set (PKAS)
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Subject analysis set type	Per protocol
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Subject analysis set description:

The PKAS included the patients who have received at least one dose of IMP and are evaluable for PK analysis : the patients who had enough samples collected to provide interpretable PK results with no deviations that might have affected the PK interpretation (e.g. infusion interrupted for any reason, deviation in the theoretical administered dose > 10%, at least one missing PK sample during the 48 first hours, ≥ 2 missing PK samples after the 48-hour time point).

Certain parameters could not be calculated if PAA went below the Lower Limit of Quantitation (LLOQ) during the 600 hr observation period.

Subject analysis set title	Immunogenicity Analysis Set (IAS)
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Subject analysis set type	Per protocol
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Subject analysis set description:

The Immunogenicity Analysis Set (IAS) will include all subjects who have received at least one dose of IMP and have at least one post-dose sample evaluable for immunogenicity testing.

Primary: Maximum Observed Plasma Asparaginase Activity (C_{max}) of S95014 After Single Dose Administration

End point title	Maximum Observed Plasma Asparaginase Activity (C _{max}) of S95014 After Single Dose Administration
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End point description:

Maximum observed plasma asparaginase activity of S95014 (Pegaspargase) in serum after single dose administration was assessed using a validated enzymatic assay method (ELISA).

End point type	Primary
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End point timeframe:

Predose up to 600 hours post dose

End point values	S95014 Lyophilizate	S95014 Liquid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	40		
Units: mU/mL				
geometric mean (geometric coefficient of variation)	1563.115 ($\pm$ 23.11)	1672.136 ($\pm$ 41.91)		

Statistical analyses

Statistical analysis title	Statistical Evaluation of Cmax
Statistical analysis description:	
Cmax was natural log-transformed and analyzed using an analysis of variance (ANOVA) with fixed effect for formulation. The two one-sided tests procedures were performed on the geometric mean ratio (GMR) between test (S95014 lyophilizate) and reference (S95014 liquid formulation) treatments. The 90% confidence interval for the ratio was obtained within the framework of the ANOVA.	
Comparison groups	S95014 Lyophilizate v S95014 Liquid
Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	equivalence ^[1]
Parameter estimate	GMR (%)
Point estimate	93.5
Confidence interval	
level	90 %
sides	2-sided
lower limit	82.9
upper limit	105.5

Notes:

[1] - PK comparability between the test treatment and the reference treatment was concluded if the 90% CI for GMR is within the [80.00%; 125.00%] range.

Primary: Area Under the Plasma Asparaginase Activity-Time Curve from Time Zero to Infinity (AUCinf) of S95014 After Single Dose Administration

End point title	Area Under the Plasma Asparaginase Activity-Time Curve from Time Zero to Infinity (AUCinf) of S95014 After Single Dose Administration
End point description:	
The value of AUCinf was considered unreliable if the terminal area beyond the last quantified sample is greater than 20% of the total AUCinf.	
End point type	Primary
End point timeframe:	
Predose up to 600 hours	

End point values	S95014 Lyophilizate	S95014 Liquid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	39 ^[2]		
Units: mU*day/mL				
geometric mean (geometric coefficient of variation)	362028.656 ($\pm$ 33.55)	352248.907 ($\pm$ 31.08)		

Notes:

[2] - AUCinf could not be calculated in one patient who had only 3 positive values exceeding the LLOQ

Statistical analyses

Statistical analysis title	Statistical Evaluation of AUCinf
Statistical analysis description:	
AUCinf was natural log-transformed and analyzed using an analysis of variance (ANOVA) with fixed effect for formulation. The two one-sided tests procedures were performed on the geometric mean ratio (GMR) between test (S95014 lyophilizate) and reference (S95014 liquid formulation) treatments. The 90% confidence interval for the ratio was obtained within the framework of the ANOVA.	
Comparison groups	S95014 Lyophilizate v S95014 Liquid
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	equivalence ^[3]
Parameter estimate	GMR (%)
Point estimate	102.8
Confidence interval	
level	90 %
sides	2-sided
lower limit	91.4
upper limit	115.6

Notes:

[3] - PK comparability between the test treatment and the reference treatment was concluded if the 90% CI for GMR is within the [80.00%; 125.00%] range.

Secondary: Observed Plasma Asparaginase Activity 14 days post-dose (Cday 14) of S95014 After Single Dose Administration

End point title	Observed Plasma Asparaginase Activity 14 days post-dose (Cday 14) of S95014 After Single Dose Administration
End point description:	
Observed plasma asparaginase activity of S95014 (Pegaspargase) in serum 14 days post dose was assessed using a validated enzymatic assay method (ELISA).	
End point type	Secondary
End point timeframe:	
Predose to day 14 post dose	

End point values	S95014 Lyophilizate	S95014 Liquid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	39 ^[4]		
Units: mU/mL				
geometric mean (geometric coefficient of variation)	496.599 (± 37.96)	408.655 (± 80.35)		

Notes:

[4] - Cday14 could not be calculated in one patient who had only 3 positive values exceeding the LLOQ

Statistical analyses

Statistical analysis title	Statistical Evaluation of Cday14
Statistical analysis description:	
Cday14 was natural log-transformed and analyzed using an analysis of variance (ANOVA) with fixed effect for formulation. The two one-sided tests procedures were performed on the geometric mean ratio (GMR) between test (S95014 lyophilizate) and reference (S95014 liquid formulation) treatments. The 90% confidence interval for the ratio was obtained within the framework of the ANOVA.	
Comparison groups	S95014 Lyophilizate v S95014 Liquid
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	equivalence ^[5]
Parameter estimate	GMR (%)
Point estimate	121.5
Confidence interval	
level	90 %
sides	2-sided
lower limit	98.7
upper limit	149.6

Notes:

[5] - PK comparability between the test treatment and the reference treatment was concluded if the 90% CI for GMR is within the [80.00%; 125.00%] range.

Secondary: Immunogenicity by measuring anti-drug antibodies (ADA) formation against S95014 and anti-PEG with the lyophilized or liquid formulations (positive patients)

End point title	Immunogenicity by measuring anti-drug antibodies (ADA) formation against S95014 and anti-PEG with the lyophilized or liquid formulations (positive patients)
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End point description:

The number of patients having anti-S95014 after the administration of either liquid or lyophilized S95014 was determined. Seroconversion upon treatment was considered if a patient converted from negative at baseline to positive at Day 17 and Day 28. If a confirmed positive sample at baseline has titer increase at Day 17 or Day 28 by at least 4-fold then it was included within the seroconverters. A patient starting with pre-existing antibodies (positive baseline) was considered for positive post-baseline anti-drug antibodies. A patient with missing baseline will be considered as negative baseline to be conservative. For all positive anti-S95014 evaluations there is an associated anti-PEG results. Post-treatment results of ADA formation against S95014 and against anti-pegaspargase are reported.

End point type	Secondary
End point timeframe:	
Pre-dose, 14 and 25 days post-dose	

End point values	S95014 Lyophilizate	S95014 Liquid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	43		
Units: number of patients				
number (not applicable)				
Anti-S95014 positive	5	4		
Anti-S95014 positive/Anti-PEG negative	3	1		
Anti-S95014 positive/Anti-PEG positive	2	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Achievement of Plasma Asparaginase Activity (PAA) of ≥ 100 mU/mL after the administration of either lyophilized or liquid S95014

End point title	Achievement of Plasma Asparaginase Activity (PAA) of ≥ 100 mU/mL after the administration of either lyophilized or liquid S95014
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End point description:

The achievement of PAA ≥ 100 mU/mL was assessed at 7, 14, 18 and 25 days after the infusion of either liquid or lyophilized S95014.

The number of patients achieving a PAA of ≥ 100 mU/mL 7, 14, 18 and 25 days after the administration of either liquid or lyophilized S95014 is reported.

End point type	Secondary
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End point timeframe:

Day 7, 14, 18 and 25 post-dose of either liquid or lyophilized S95014

End point values	S95014 Lyophilizate	S95014 Liquid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	45		
Units: number of patients				
number (not applicable)				
Day 10 PAA ≥ 100 mU/mL (n=44 LIQ)	43	43		
Day 17 PAA ≥ 100 mU/mL (n=43 LIQ)	43	41		
Day 21 PAA ≥ 100 mU/mL (n=43 LIQ, n=42 LYO)	41	39		
Day 28 PAA ≥ 100 mU/mL (n=43 LIQ, n=42 LYO)	18	6		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment emergent AEs were recorded from IMP administration on Day 3, until the withdrawal/end-of-study visit, which was at least 30 days after S95014 infusion, and before starting the consolidation phase.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups

Reporting group title	S95014 Lyophilizate
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Reporting group description: -

Reporting group title	S95014 Liquid
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Reporting group description: -

Serious adverse events	S95014 Lyophilizate	S95014 Liquid	
Total subjects affected by serious adverse events			
subjects affected / exposed	19 / 43 (44.19%)	18 / 45 (40.00%)	
number of deaths (all causes)	1	2	
number of deaths resulting from adverse events	1	2	
Investigations			
Lymphocyte count decreased			
subjects affected / exposed	3 / 43 (6.98%)	4 / 45 (8.89%)	
occurrences causally related to treatment / all	1 / 3	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count decreased			
subjects affected / exposed	4 / 43 (9.30%)	2 / 45 (4.44%)	
occurrences causally related to treatment / all	3 / 4	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Antithrombin III decreased			
subjects affected / exposed	2 / 43 (4.65%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood fibrinogen decreased			

subjects affected / exposed	2 / 43 (4.65%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alanine aminotransferase increased			
subjects affected / exposed	1 / 43 (2.33%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 43 (2.33%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
subjects affected / exposed	0 / 43 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	1 / 43 (2.33%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	0 / 43 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Protein S decreased			
subjects affected / exposed	1 / 43 (2.33%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	0 / 43 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			

subjects affected / exposed	1 / 43 (2.33%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Pelvic venous thrombosis			
subjects affected / exposed	1 / 43 (2.33%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superior vena cava syndrome			
subjects affected / exposed	0 / 43 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Brain oedema			
subjects affected / exposed	0 / 43 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain stem stroke			
subjects affected / exposed	0 / 43 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Posterior reversible encephalopathy syndrome			
subjects affected / exposed	1 / 43 (2.33%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 43 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonic convulsion			
subjects affected / exposed	0 / 43 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	3 / 43 (6.98%)	5 / 45 (11.11%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	4 / 43 (9.30%)	4 / 45 (8.89%)	
occurrences causally related to treatment / all	1 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypofibrinogenaemia			
subjects affected / exposed	1 / 43 (2.33%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphopenia			
subjects affected / exposed	1 / 43 (2.33%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	2 / 43 (4.65%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated intravascular coagulation			
subjects affected / exposed	0 / 43 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 43 (2.33%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Multiple organ dysfunction syndrome			

subjects affected / exposed	1 / 43 (2.33%)	2 / 45 (4.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Catheter site thrombosis			
subjects affected / exposed	0 / 43 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Neutropenic colitis			
subjects affected / exposed	3 / 43 (6.98%)	4 / 45 (8.89%)	
occurrences causally related to treatment / all	1 / 3	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedematous pancreatitis			
subjects affected / exposed	2 / 43 (4.65%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis haemorrhagic			
subjects affected / exposed	0 / 43 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 43 (2.33%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctitis			
subjects affected / exposed	0 / 43 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	2 / 43 (4.65%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatosplenomegaly			

subjects affected / exposed	1 / 43 (2.33%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatotoxicity			
subjects affected / exposed	1 / 43 (2.33%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Interstitial lung disease			
subjects affected / exposed	1 / 43 (2.33%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	2 / 43 (4.65%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	2 / 43 (4.65%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Appendicitis			
subjects affected / exposed	1 / 43 (2.33%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Candida pneumonia			
subjects affected / exposed	1 / 43 (2.33%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	1 / 43 (2.33%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastroenteritis norovirus subjects affected / exposed	1 / 43 (2.33%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal bacterial infection subjects affected / exposed	1 / 43 (2.33%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis subjects affected / exposed	1 / 43 (2.33%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomembranous colitis subjects affected / exposed	1 / 43 (2.33%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock subjects affected / exposed	0 / 43 (0.00%)	1 / 45 (2.22%)	
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	S95014 Lyophilizate	S95014 Liquid	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	43 / 43 (100.00%)	44 / 45 (97.78%)	
Investigations			
Blood fibrinogen decreased subjects affected / exposed	33 / 43 (76.74%)	37 / 45 (82.22%)	
occurrences (all)	33	39	
Antithrombin III decreased subjects affected / exposed	30 / 43 (69.77%)	31 / 45 (68.89%)	
occurrences (all)	30	31	
Lymphocyte count decreased			

subjects affected / exposed	29 / 43 (67.44%)	23 / 45 (51.11%)
occurrences (all)	31	29
White blood cell count decreased		
subjects affected / exposed	15 / 43 (34.88%)	13 / 45 (28.89%)
occurrences (all)	15	13
Alanine aminotransferase increased		
subjects affected / exposed	8 / 43 (18.60%)	17 / 45 (37.78%)
occurrences (all)	9	18
Blood bilirubin increased		
subjects affected / exposed	13 / 43 (30.23%)	11 / 45 (24.44%)
occurrences (all)	14	11
Protein S decreased		
subjects affected / exposed	9 / 43 (20.93%)	9 / 45 (20.00%)
occurrences (all)	9	9
Aspartate aminotransferase increased		
subjects affected / exposed	6 / 43 (13.95%)	10 / 45 (22.22%)
occurrences (all)	6	10
Ammonia increased		
subjects affected / exposed	5 / 43 (11.63%)	6 / 45 (13.33%)
occurrences (all)	5	6
Gamma-glutamyltransferase increased		
subjects affected / exposed	4 / 43 (9.30%)	7 / 45 (15.56%)
occurrences (all)	4	7
Platelet count decreased		
subjects affected / exposed	4 / 43 (9.30%)	4 / 45 (8.89%)
occurrences (all)	4	4
Activated partial thromboplastin time prolonged		
subjects affected / exposed	5 / 43 (11.63%)	1 / 45 (2.22%)
occurrences (all)	5	1
Blood albumin decreased		
subjects affected / exposed	2 / 43 (4.65%)	4 / 45 (8.89%)
occurrences (all)	2	4
International normalised ratio increased		

subjects affected / exposed occurrences (all)	3 / 43 (6.98%) 3	2 / 45 (4.44%) 2	
Neutrophil count decreased subjects affected / exposed occurrences (all)	2 / 43 (4.65%) 2	3 / 45 (6.67%) 4	
Blood urea increased subjects affected / exposed occurrences (all)	3 / 43 (6.98%) 4	1 / 45 (2.22%) 1	
Haemoglobin decreased subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1	3 / 45 (6.67%) 3	
Nervous system disorders			
Toxic neuropathy subjects affected / exposed occurrences (all)	11 / 43 (25.58%) 11	6 / 45 (13.33%) 6	
Neuropathy peripheral subjects affected / exposed occurrences (all)	3 / 43 (6.98%) 3	1 / 45 (2.22%) 1	
Headache subjects affected / exposed occurrences (all)	3 / 43 (6.98%) 3	0 / 45 (0.00%) 0	
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	10 / 43 (23.26%) 10	16 / 45 (35.56%) 17	
Thrombocytopenia subjects affected / exposed occurrences (all)	8 / 43 (18.60%) 8	13 / 45 (28.89%) 13	
Leukopenia subjects affected / exposed occurrences (all)	12 / 43 (27.91%) 12	8 / 45 (17.78%) 8	
Neutropenia subjects affected / exposed occurrences (all)	6 / 43 (13.95%) 6	8 / 45 (17.78%) 10	
Hypofibrinogenaemia			

subjects affected / exposed occurrences (all)	4 / 43 (9.30%) 5	3 / 45 (6.67%) 3	
Lymphopenia subjects affected / exposed occurrences (all)	2 / 43 (4.65%) 2	5 / 45 (11.11%) 5	
Gastrointestinal disorders			
Stomatitis subjects affected / exposed occurrences (all)	5 / 43 (11.63%) 5	5 / 45 (11.11%) 5	
Diarrhoea subjects affected / exposed occurrences (all)	4 / 43 (9.30%) 4	2 / 45 (4.44%) 2	
Abdominal pain subjects affected / exposed occurrences (all)	3 / 43 (6.98%) 3	1 / 45 (2.22%) 1	
Neutropenic colitis subjects affected / exposed occurrences (all)	3 / 43 (6.98%) 3	0 / 45 (0.00%) 0	
Hepatobiliary disorders			
Hyperbilirubinaemia subjects affected / exposed occurrences (all)	4 / 43 (9.30%) 5	1 / 45 (2.22%) 1	
Metabolism and nutrition disorders			
Hypoalbuminaemia subjects affected / exposed occurrences (all)	10 / 43 (23.26%) 10	8 / 45 (17.78%) 9	
Hypocalcaemia subjects affected / exposed occurrences (all)	5 / 43 (11.63%) 5	2 / 45 (4.44%) 2	
Hyperglycaemia subjects affected / exposed occurrences (all)	3 / 43 (6.98%) 3	0 / 45 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 December 2020	It mainly concerned the study protocol following Food & Drug Administration (FDA) non-hold comments: - Clarification about the collection of PK and PAA samples - Addition of an immunogenicity timepoint 14 days post-dose (Day 17) - Clarification about the sample size calculation - Addition of 14-day post-dose time point (CDay14) as a PK secondary endpoint - Deletion of a specific dosing regimen of 82.5 U/kg for patients with low BSA - Additional minor changes

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported