Clinical trial results:
A multicentre, roll-over study to provide continued treatment with lyophilized pegaspargase (S95014) in Pediatric Patients with Acute Lymphoblastic Leukemia (ALL)

Summary

EudraCT number	2020-004895-17
Trial protocol	Outside EU/EEA
Global end of trial date	23 January 2023

Results information

Result version number	v1 (current)
This version publication date	26 July 2023
First version publication date	26 July 2023

Trial information

Trial identification

Sponsor protocol code	CL2-95014-003

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04956666
WHO universal trial number (UTN)	-
Other trial identifiers	Investigational New Drug Application No.: 152743

Notes:

Sponsors

Sponsor organisation name	Institut de Recherches Internationales Servier and Les Laboratoires Servier (L.L.S.)
Sponsor organisation address	50 rue Carnot, Suresnes Cedex, France, 92284
Public contact	Clinical Studies Department, Institut de Recherches Internationales Servier, +33 155724366, clinicaltrials@servier.com
Scientific contact	Clinical Studies Department, 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	18 April 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 January 2023
Global end of trial reached?	Yes
Global end of trial date	23 January 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To provide treatment with lyophilized S95014 in pediatric patients with ALL who completed the CL2-95014-002 study during the induction phase.

Protection of trial subjects:

The study was performed in accordance with the ethical principles stated in the Declaration of Helsinki 1964, as revised in Fortaleza, 2013 with the good clinical practice (GCP) and with the applicable regulatory requirements.
Each patient, in the presence of their parent(s) / legal guardians, was informed by the investigator (or their delegate) to the fullest extent possible about the details of the study in language and terms they could understand. The patients were also informed that they had the possibility not to participate in the study and that they were free to reconsider their assent at any time.

Background therapy:

The following treatments were to be used with caution during the whole treatment phase:
- Coumarin/warfarin and heparin, dipyridamole, acetylsalicylic acid or non-steroidal anti-inflammatory medicines (e.g. ibuprofen, naproxen)
- Prednisone, methotrexate, vincristine, cytarabine.
The main pharmacological classes of concomitant treatments, listed by decreasing frequency of use, were:
- 70% or more patients: antiemetics and antinauseants, antibacterials for systemic use, blood substitutes and perfusion solutions.
- 60% to 70% of patients: corticosteroids for systemic use, antihistamines for systemic use, antithrombotic agents.
- 40% to 60% of patients: drugs for acid related disorders, mineral supplements, bile and liver therapy, antimycotics for systemic use, antianemic preparations.
- 20% to 40% of patients: antivirals for systemic use, analgesics, digestives, incl. enzymes, antihemorrhagics, psychoanaleptics, immunostimulants, other alimentary tract and metabolism products.
- 10% to 20% of patients: cardiac therapy, drugs for constipation, drugs for functional gastrointestinal disorders, psycholeptics, stomatological preparations, vitamins, and anti-inflammatory and antirheumatic products, other nervous system drugs, immune sera and immunoglobulins.

Evidence for comparator:

Not applicable

Actual start date of recruitment	15 May 2021
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	1 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Russian Federation: 74
Worldwide total number of subjects	74
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)	0
Children (2-11 years)	66
Adolescents (12-17 years)	7
Adults (18-64 years)	1
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

All investigators were oncologists.

Pre-assignment

Screening details:

Patients who completed the CL2-95014-002 study and received clinical benefit from previous treatment with S95014 as per investigator's judgment, were included in the current CL2-95014-003 study. Other main criteria for inclusion in the study were signed informed consent and assent (where appropriate) and highly effective contraception method.

Period 1

Period 1 title	Treatment period (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

This was a non-randomized, open-label, roll-over study of S95014 lyophilizate during the consolidation phase of pediatric patients with ALL.

Arms

Arm title	Consolidation phase

Arm description:

In this study, patients were treated for the consolidation phase and received the backbone chemotherapy agents outlined in the ALL-MB 2015 protocol. The patients were assigned to receive lyophilized pegaspargase (S95014) which was administered on 9 occasions, at weeks 7, 9, 11, 15, 17, 19, 23, 25 and 27 (3 phases S1, S2 and S3) over 1-hour IV infusion, at a dose of 1000 U/m².

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

Dosage and administration details:

S95014 lyophilizate was reconstituted with sterile water for intravenous (IV) administration and was administered every two weeks during the consolidation phase for a total of 9 infusions, at weeks 7, 9, 11, 15, 17, 19, 23, 25 and 27, at a dose of 1000 U/m².

Number of subjects in period 1	Consolidation phase
Started	74
Completed	52
Not completed	22
Physician decision	4
Adverse event, non-fatal	18

Baseline characteristics

Reporting groups

Reporting group title	Consolidation phase

Reporting group description:

In this study, patients were treated for the consolidation phase and received the backbone chemotherapy agents outlined in the ALL-MB 2015 protocol. The patients were assigned to receive lyophilized pegaspargase (S95014) which was administered on 9 occasions, at weeks 7, 9, 11, 15, 17, 19, 23, 25 and 27 (3 phases S1, S2 and S3) over 1-hour IV infusion, at a dose of 1000 U/m².

Reporting group values	Consolidation phase	Total	
Number of subjects	74	74	
Age categorical Units: Subjects			
Children (2-11 years)	66	66	
Adolescents (12-17 years)	7	7	
Adults (18-64 years)	1	1	
Age continuous Units: years			
arithmetic mean	6.1		
standard deviation	± 3.8	-	
Gender categorical Units: Subjects			
Female	36	36	
Male	38	38	

Subject analysis sets

Subject analysis set title	Safety Analysis Set
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety Analysis Set (SAS) was defined as the set of all patients who had received at least one dose of S95014.

Reporting group values	Safety Analysis Set		
Number of subjects	74		
Age categorical Units: Subjects			
Children (2-11 years)	66		
Adolescents (12-17 years)	7		
Adults (18-64 years)	1		
Age continuous Units: years			
arithmetic mean	6.1		
standard deviation	± 3.8		
Gender categorical Units: Subjects			
Female	36		
Male	38		

End points

End points reporting groups

Reporting group title	Consolidation phase

Reporting group description:

In this study, patients were treated for the consolidation phase and received the backbone chemotherapy agents outlined in the ALL-MB 2015 protocol. The patients were assigned to receive lyophilized pegaspargase (S95014) which was administered on 9 occasions, at weeks 7, 9, 11, 15, 17, 19, 23, 25 and 27 (3 phases S1, S2 and S3) over 1-hour IV infusion, at a dose of 1000 U/m².

Subject analysis set title	Safety Analysis Set
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety Analysis Set (SAS) was defined as the set of all patients who had received at least one dose of S95014.

Primary: Extent of exposure

End point title	Extent of exposure[1]

End point description:

All 74 patients received at least one dose of S95014 (1000 U/m²). A single dose was received by 7 patients, 2 doses only were received by 10 patients, and 3 doses only were received by 3 patients; Thus, 20/74 patients (27%) received 3 doses or less. Except for 2 patients who received 8 doses, the remaining patients (52/74 [70%]) received 9 doses, as per protocol.
The number of doses administered was 7.0 Mean ± 3.23 SD (median: 9).

End point type	Primary

End point timeframe:

From the Inclusion visit until the last S95014 infusion.

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 analyses have been provided since data was summarized using descriptive statistics.

End point values	Consolidation phase	Safety Analysis Set		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	74	74		
Units: months				
arithmetic mean (standard deviation)				
Duration of treatment	5.0 (± 2.59)	5.0 (± 2.59)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the Inclusion visit up until 30 days after the last S95014 infusion or the date of withdrawal, whichever is earlier.

Adverse event reporting additional description:

Treatment-emergent adverse event (TEAE) was defined as any untoward medical occurrence in a patient who received the IMP. The serious TEAEs include those upgraded by the Sponsor. No new safety concerns for S95014 were detected and it was well tolerated. No fatal events were reported during the study.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups

Reporting group title	Consolidation phase

Reporting group description: -

Serious adverse events	Consolidation phase		
Total subjects affected by serious adverse events			
subjects affected / exposed	27 / 74 (36.49%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Ejection fraction decreased			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neutrophil count decreased			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	5 / 74 (6.76%)		
occurrences causally related to treatment / all	1 / 6		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			

subjects affected / exposed	4 / 74 (5.41%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Agranulocytosis				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Anaemia				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Leukopenia				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
General physical health deterioration				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Immune system disorders				
Hypersensitivity				
subjects affected / exposed	11 / 74 (14.86%)			
occurrences causally related to treatment / all	12 / 12			
deaths causally related to treatment / all	0 / 0			
Anaphylactic reaction				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Drug hypersensitivity				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			

Haemophagocytic lymphohistiocytosis			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Enterocolitis haemorrhagic			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oedematous pancreatitis			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreatitis			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hepatomegaly			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatotoxicity			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
COVID-19			

subjects affected / exposed	3 / 74 (4.05%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Bronchitis				
subjects affected / exposed	2 / 74 (2.70%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
COVID-19 pneumonia				
subjects affected / exposed	2 / 74 (2.70%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	2 / 74 (2.70%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Appendicitis				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cellulitis gangrenous				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Device related bacteraemia				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Device related infection				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Laryngitis				

subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neutropenic sepsis			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pneumonia fungal			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Consolidation phase		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	68 / 74 (91.89%)		
Investigations			
Antithrombin III decreased			
subjects affected / exposed	53 / 74 (71.62%)		
occurrences (all)	161		
Blood fibrinogen decreased			
subjects affected / exposed	48 / 74 (64.86%)		
occurrences (all)	118		
Alanine aminotransferase increased			
subjects affected / exposed	35 / 74 (47.30%)		
occurrences (all)	48		
Gamma-glutamyltransferase increased			
subjects affected / exposed	31 / 74 (41.89%)		
occurrences (all)	31		
Aspartate aminotransferase increased			
subjects affected / exposed	24 / 74 (32.43%)		
occurrences (all)	28		
Protein S decreased			

subjects affected / exposed	12 / 74 (16.22%)		
occurrences (all)	17		
Blood bilirubin increased			
subjects affected / exposed	11 / 74 (14.86%)		
occurrences (all)	11		
Neutrophil count decreased			
subjects affected / exposed	10 / 74 (13.51%)		
occurrences (all)	16		
White blood cell count decreased			
subjects affected / exposed	8 / 74 (10.81%)		
occurrences (all)	8		
Activated partial thromboplastin time prolonged			
subjects affected / exposed	7 / 74 (9.46%)		
occurrences (all)	8		
Lipase increased			
subjects affected / exposed	6 / 74 (8.11%)		
occurrences (all)	8		
Blood albumin decreased			
subjects affected / exposed	4 / 74 (5.41%)		
occurrences (all)	5		
Haemoglobin decreased			
subjects affected / exposed	4 / 74 (5.41%)		
occurrences (all)	4		
Nervous system disorders			
Toxic neuropathy			
subjects affected / exposed	5 / 74 (6.76%)		
occurrences (all)	5		
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	49 / 74 (66.22%)		
occurrences (all)	105		
Anaemia			
subjects affected / exposed	33 / 74 (44.59%)		
occurrences (all)	47		
Leukopenia			

subjects affected / exposed	20 / 74 (27.03%)		
occurrences (all)	26		
Thrombocytopenia			
subjects affected / exposed	11 / 74 (14.86%)		
occurrences (all)	14		
Hypofibrinogenaemia			
subjects affected / exposed	4 / 74 (5.41%)		
occurrences (all)	6		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	7 / 74 (9.46%)		
occurrences (all)	10		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	15 / 74 (20.27%)		
occurrences (all)	20		
Drug hypersensitivity			
subjects affected / exposed	5 / 74 (6.76%)		
occurrences (all)	6		
Infections and infestations			
COVID-19			
subjects affected / exposed	7 / 74 (9.46%)		
occurrences (all)	7		
Upper respiratory tract infection			
subjects affected / exposed	4 / 74 (5.41%)		
occurrences (all)	7		
Metabolism and nutrition disorders			
Hypoalbuminaemia			
subjects affected / exposed	14 / 74 (18.92%)		
occurrences (all)	20		
Hypoglycaemia			
subjects affected / exposed	5 / 74 (6.76%)		
occurrences (all)	7		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Not applicable

Notes: