Clinical trial results:
An Open-label, Single-arm, Multi-center Study to Evaluate the Efficacy and Safety of Rasburicase (Fasturtec®) in the Prevention and Treatment of Hyperuricemia in Pediatric Patients with Non-Hodgkin's Lymphoma and Acute Leukemia

Summary

EudraCT number	2021-003176-14
Trial protocol	Outside EU/EEA
Global end of trial date	12 March 2021

Results information

Result version number	v1 (current)
This version publication date	14 September 2021
First version publication date	14 September 2021

Trial information

Trial identification

Sponsor protocol code	LPS15679

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04349306
WHO universal trial number (UTN)	U1111-1233-0737
Other trial identifiers	Study name: RAISE, Study code number: RASBUL09107

Notes:

Sponsors

Sponsor organisation name	Sanofi aventis recherche & développement
Sponsor organisation address	1 avenue Pierre Brossolette , Chilly-Mazarin, France, 91380
Public contact	Trial Transparency Team, Sanofi aventis recherche & développement, contact-US@sanofi.com
Scientific contact	Trial Transparency Team, Sanofi aventis recherche & développement, contact-US@sanofi.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	30 April 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	12 March 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the safety of Rasburicase in pediatric subjects with Non-Hodgkin’s Lymphoma (NHL) and Acute Leukemia (AL).

Protection of trial subjects:

The study was conducted by investigators experienced in the treatment of paediatric patients. The parent(s) or guardian(s) as well as the children were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time. In addition to the consent form for the parent(s)/guardian(s), an assent form in child-appropriate language was provided and explained to the child. Repeated invasive
procedures were minimised. The number of blood samples as well as the amount of blood drawn were adjusted according to age and weight. A topical anesthesia might have been used to minimise distress and discomfort.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 May 2020
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	China: 50
Worldwide total number of subjects	50
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)	44
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:

Study was conducted at 10 study centers in China. A total of 55 subjects were screened between 14 May 2020 and 26-February-2021, of which 5 subjects were screen failures. Screen failures were mainly due to met the exclusion criteria.

Pre-assignment

Screening details:

1 subject excluded from enrolled population due to major protocol deviation (met the exclusion criteria) was included in the safety population.

Period 1

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

Arms

Arm title	Rasburicase

Arm description:

Subjects received Rasburicase 0.20 milligram per kilogram per day (mg/kg/day) by intravenous (IV) infusion over 30 minutes from Day 1 to Day 5.

Arm type	Experimental
Investigational medicinal product name	Rasburicase
Investigational medicinal product code	SR29142
Other name	Fasturtec®
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

0.20 mg/kg/day by intravenous infusion over 30 minutes for Day 1 to Day 5.

Number of subjects in period 1[1]	Rasburicase
Started	49
Completed	46
Not completed	3
Physician decision	2
Withdrawal by Subject	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: 1 subject excluded from enrolled population due to major protocol deviation (met the exclusion criteria).

Baseline characteristics

Reporting groups	
Reporting group title	Rasburicase

Reporting group description:

Subjects received Rasburicase 0.20 milligram per kilogram per day (mg/kg/day) by intravenous (IV) infusion over 30 minutes from Day 1 to Day 5.

Reporting group values	Rasburicase	Total	
Number of subjects	49	49	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 6.9 ± 3.39	 -	
Gender categorical Units: Subjects			
Female	15	15	
Male	34	34	

End points

End points reporting groups

Reporting group title	Rasburicase

Reporting group description:

Subjects received Rasburicase 0.20 milligram per kilogram per day (mg/kg/day) by intravenous (IV) infusion over 30 minutes from Day 1 to Day 5.

Subject analysis set title	Rasburicase
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects received Rasburicase 0.20 mg/kg/day by IV infusion over 30 minutes from Day 1 to Day 5.

Primary: Number of Subjects With Treatment-Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs)

End point title	Number of Subjects With Treatment-Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs)[1]

End point description:

An adverse event (AE) was any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. The TEAEs were defined as AEs that occurred, worsened or became serious during the TEAE period (from first dose of study drug until 48 hours after last dose of study treatment [up to Day 7]). SAE was any untoward medical occurrence that at any dose resulted in death or was life-threatening or required inpatient hospitalisation or prolongation of existing hospitalisation or resulted in persistent or significant disability/incapacity or was a congenital anomaly/birth defect or was a medically important event. Analysis was performed on the safety population, which included subjects who received at least one dose of investigational medicinal product (IMP).

End point type	Primary

End point timeframe:

From Day 1 up to Day 7

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: Since the endpoint was descriptive in nature, no statistical analysis was provided.

End point values	Rasburicase			
Subject group type	Subject analysis set			
Number of subjects analysed	50			
Units: subject				
number (not applicable)				
TEAEs	25			
SAE	4			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Achieving Normal Uric Acid Levels (<= 8.0 mg/dL) Among Subjects Whose Plasma Uric Acid Levels are >8.0 mg/dL at Baseline

End point title	Number of Subjects Achieving Normal Uric Acid Levels (<= 8.0

	mg/dL) Among Subjects Whose Plasma Uric Acid Levels are >8.0 mg/dL at Baseline

End point description:

Response was defined as achievement of normal uric acid levels (less than or equal to [<=] 8.0 milligram per deciliter [mg/dL]) in the subjects whose uric acid levels were greater than (>) 8.0 mg/dL. Analysis was performed on the intent-to treat (ITT) population which included all enrolled subjects who had received at least one dose of IMP and had one post-treatment assessment of plasma uric acid. Here, 'number of subjects analysed' = subjects with available data for this endpoint. Here, "n"= subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

From first administration to 120 hours after the first dose

End point values	Rasburicase			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: subject				
number (not applicable)				
Day 1 (n= 19)	17			
Day 2 (n= 19)	19			
Day 3 (n= 19)	17			
Day 4 (n= 18)	18			
Day 5 (n= 18)	18			
Day 6 (n=18)	17			
Overall (n=19)	19			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Who Maintain the Normal Uric Acid Levels Among Subjects Whose Baseline Plasma Uric Acid Levels Were <= 8 mg/dL

End point title	Percentage of Subjects Who Maintain the Normal Uric Acid Levels Among Subjects Whose Baseline Plasma Uric Acid Levels Were <= 8 mg/dL

End point description:

Analysis was performed on the ITT population. Here, 'number of subjects analysed' = subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

From first administration to 120 hours after the first dose

End point values	Rasburicase			
Subject group type	Reporting group			
Number of subjects analysed	29			
Units: percentage of subjects				
number (not applicable)	86.2			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Percent Change From Baseline in Plasma Uric Acid Level

End point title	Maximum Percent Change From Baseline in Plasma Uric Acid Level

End point description:

Maximum change in Plasma Uric Acid was calculated by subtracting Baseline value from lowest value divided by Baseline value multiplied by 100. Analysis was performed on the ITT population. Here, 'n'= subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

From first administration to 120 hours after the first dose

End point values	Rasburicase			
Subject group type	Reporting group			
Number of subjects analysed	48			
Units: percent change				
arithmetic mean (standard deviation)				
Day 1 (n=29)	-94.7868 (± 4.6233)			
Day 2 (n=29)	-82.7368 (± 23.3945)			
Day 3 (n=28)	-82.1705 (± 24.1585)			
Day 4 (n=29)	-75.7560 (± 34.9937)			
Day 5 (n=28)	-61.8480 (± 44.9627)			
Day 6 (n=28)	-52.2155 (± 51.5712)			
Maximum Decrease Visit (n= 29)	-96.6969 (± 3.4990)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Reported AEs are TEAEs that developed/worsened or became serious during the TEAE period (from first dose of study drug until 48 hours after last dose of study treatment [up to Day 7]).

Adverse event reporting additional description:

Analysis was performed on the safety population. 1 subject excluded from enrolled population due to major protocol deviation (met the exclusion criteria) was included in the safety population.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	Rasburicase

Reporting group description:

Subjects received Rasburicase 0.20 mg/kg/day by IV infusion over 30 minutes from Day 1 to Day 5.

Serious adverse events	Rasburicase		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 50 (8.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Refractoriness to platelet transfusion			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Anaphylactic shock			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			

Tumour lysis syndrome			
subjects affected / exposed	1 / 50 (2.00%)		
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	Rasburicase		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 50 (40.00%)		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	4 / 50 (8.00%)		
occurrences (all)	4		
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 50 (8.00%)		
occurrences (all)	4		
White blood cell count decreased			
subjects affected / exposed	4 / 50 (8.00%)		
occurrences (all)	4		
Neutrophil count decreased			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	3		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	6 / 50 (12.00%)		
occurrences (all)	6		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	3		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	3		
Nausea			

subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	3 / 50 (6.00%) 3 3 / 50 (6.00%) 3		
Hepatobiliary disorders Hepatic function abnormal subjects affected / exposed occurrences (all)	 3 / 50 (6.00%) 3		
Metabolism and nutrition disorders Hypokalaemia subjects affected / exposed occurrences (all)	 5 / 50 (10.00%) 5		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 June 2019	Following changes were made: Combined inclusion criteria 4 and 5 in to one sentence; changed the high risk of tumor lysis syndrome (TLS) definition of AL subjects from "A. white blood cell (WBC) greater than or equal to (>=) 10.0*10^9/L, or B. WBC less than (<)10.0* 10^9/L with C. lactate dehydrogenase (LDH) >=2* upper limit of normal (ULN)" to "A. WBC >=100.0* 10^9/L, or B. WBC <100.0* 10^9/L with LDH >=28 ULN"; deleted "and with life expectancy of >3 months" in the last inclusion criteria; changed the inclusion criteria 4 from "newly diagnosed NHL or AL; or during the intermission of chemotherapy at screening with hyperuricemia: blood uric acid >8 mg/dL (473 micromole per liter [mcmol/L])." to "newly diagnosed NHL or AL who was at the initiation of or during the first cycle of chemotherapy, baseline blood uric acid >8 mg/dL (473 mcmol/L) at screening"; changed inclusion criteria 5 from "If newly diagnosed NHL subject with blood uric acid <=8 mg/dL at screening, the subject might diagnosed with Stage III or IV NHL with high tumor burden defined, with one or more of following below" to "If newly diagnosed NHL subject with blood uric acid <=8 mg/dL at screening, the subject might diagnosed with stage III or IV NHL with high tumor burden which would high risk of TLS defined; added "lactate dehydrogenase", full name of LDH, before LDH in inclusion criteria 5-C; changed the high risk of TLS definition of AL subject from "A. WBC >=10.0* 10^9/L, or B. WBC <10.0* 10^9/L with LDH >=2* ULN" to "A. WBC >=100.0* 10^9/L, or B. WBC <100.0* 10^9/L with LDH >=28 ULN"; changed the sponsor from "Shanghai Branch of Sanofi (China) Investment Co., Ltd." to "Sanofi (Beijing) pharmaceutical co., LTD"; changed the address from "F19, Tower 3, Kerry Center, 1228 Middle Yan'an Road, Shanghai, China" to "Haihang Industrial building, No. 108 Jian Guo Road, Chaoyang District, Beijing 100022, China"; delete "Tel: 021-22266666 Fax: 021-62880569".
29 September 2019	Following changes were made: Changed the endpoints from "For subject who aged <10 years old, written informed consent form (ICF) of subject/legal guardian (as appropriate) was required. For subject who aged 10-18 (inclusive), both written ICF of minor assent form and subject/legal guardian are required." to For subject who aged <8 years old, written ICF of subject/legal guardian (as appropriate) is required. For subject who aged 8-18 (inclusive), both written ICF of minor assent interruptions form and subject/legal guardian are required; Added "Previous glucose-6-phosphate dehydrogenase testing result was acceptable.
08 May 2020	Following changes were made: Changed the endpoint(s) from "In those subject whose baseline plasma uric acid levels are <=8 mg/dL but with a high risk of TLS, the proportion of subject who can maintain the normal uric acid levels throughout the study (from first administration to the end of follow-up: 14 days after the first administration)" to "In those subject whose Baseline plasma uric acid levels are <=8 mg/dL but with a high risk of TLS, the proportion of subject who can maintain the normal uric acid levels throughout the study (from first administration to the end of follow-up: 7 days after the first administration)"; Changed the procedures of collecting and measuring the uric acid blood sample from "Draw 1 milliliter (mL) whole blood for each collection tube" to "Draw 4 mL whole blood for each collection tube"; Added "This was a post market commitment study and the design of this protocol was served the same commitment purpose of study protocol number "RASBUL06535", which was cited by national master processing agreement in the imported drug license NO.S20180024"in introduction and rational.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported