

**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 [\leq] 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 \leq 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 \leq 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) | 3 / 50 (6.00%) 3 | | |
| Vomiting subjects affected / exposed occurrences (all) | 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 | <p>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 (\geq) $10.0 \times 10^9/L$, or B. WBC less than ($<$) $10.0 \times 10^9/L$ with C. lactate dehydrogenase (LDH) $\geq 2 \times$ upper limit of normal (ULN)" to "A. WBC $\geq 100.0 \times 10^9/L$, or B. WBC $< 100.0 \times 10^9/L$ 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 $\geq 10.0 \times 10^9/L$, or B. WBC $< 10.0 \times 10^9/L$ with LDH $\geq 2 \times$ ULN" to "A. WBC $\geq 100.0 \times 10^9/L$, or B. WBC $< 100.0 \times 10^9/L$ 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".</p> |
| 29 September 2019 | <p>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.</p> |
| 08 May 2020 | <p>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.</p> |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported