Clinical trial results:
Phase IV Study of Rasburicase for Treatment of Hyperuricemia in Patients With Tumoral Lysis Syndrome

Summary

EudraCT number	2014-003989-24
Trial protocol	Outside EU/EEA
Global end of trial date	26 January 2007

Results information

Result version number	v1 (current)
This version publication date	01 April 2016
First version publication date	18 July 2015

Trial information

Trial identification

Sponsor protocol code	L_9436

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00302653
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Sanofi-aventis Farmacêutica Ltda
Sponsor organisation address	Avenida Major Sylvio de Magalhães Padilha, 5.200. Edifício Atlanta - Jd. Morumbi , São Paulo, Brazil, 05693-000
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	15 March 2009
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 January 2007
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study was to determine if rasburicase was effective and safety to treat subjects with hyperuricemia.

Protection of trial subjects:

The study was conducted by investigators experienced in the treatment of pediatric subjects. 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 minimized. The number of blood samples as well as the amount of blood drawn were adjusted according to age and weight. A topical anesthesia may have been used to minimize distress and discomfort.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 February 2006
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	Brazil: 33
Worldwide total number of subjects	33
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)	22
Adolescents (12-17 years)	9
Adults (18-64 years)	0
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were enrolled at 3 sites in Brazil between 16 February 2006 and 30 October 2006.

Pre-assignment

Screening details:

A total of 33 subjects were screened of whom 32 subjects were treated.

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:

Rasburicase for 3-7 days.

Arm type	Experimental
Investigational medicinal product name	Rasburicase
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Rasburicase 0.20 mg/kg once a day.

Number of subjects in period 1	Rasburicase
Started	33
Treated	32
Completed	26
Not completed	7
Transference to other institution	1
Death	6

Baseline characteristics

Reporting groups	
Reporting group title	Rasburicase
Reporting group description:	
Rasburicase for 3-7 days.	

Reporting group values	Rasburicase	Total	
Number of subjects	33	33	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	8.4		
standard deviation	± 4.7	-	
Gender categorical Units: Subjects			
Female	18	18	
Male	15	15	
Race Units: Subjects			
Caucasian	13	13	
Black	1	1	
Black-caucasian biracial	19	19	
Diagnosis Units: Subjects			
Leukemia	21	21	
Lymphoma	10	10	
Other (Neuroblastoma)	2	2	

End points

End points reporting groups

Reporting group title	Rasburicase
Reporting group description:	
Rasburicase for 3-7 days.	

Primary: Percentage of Subjects with Uric Acid Levels- ITT Population and PP Population

End point title	Percentage of Subjects with Uric Acid Levels- ITT Population and PP Population[1]

End point description:

Intention-To-Treat (ITT) population included all subjects who received at least one dose of rasburicase, performed baseline and 24-48 hours or 28± 3 days uric acid exam. Per-Protocol (PP) Population included all subjects who received at least one dose of rasburicase, performed baseline and 24-48 hours uric acid exams and did not fit in any relevant protocol violation criteria. Analysis was performed on ITT and PP population. Under NRV indicated that uric acid levels were below the normal reference values and upper NRV indicated uric acid levels were above the normal reference values.

End point type	Primary

End point timeframe:

24-48 hours

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: Statistical analysis could not be provided due to EudraCT format constraint for single arm study.

End point values	Rasburicase			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: percentage of subjects				
number (not applicable)				
ITT Population: Under NRV (n=21)	90.5			
ITT Population: Normal (n=21)	4.8			
ITT Population: Upper NRV (n=21)	0			
ITT Population: Undefined/undetectable (n=21)	4.8			
PP Population: Under NRV (n=20)	90			
PP Population: Normal (n=20)	5			
PP Population: Upper NRV (n=20)	0			
PP Population: Undefined/undetectable (n=20)	5			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects with Uric Acid Levels- ITT Population and PP Population

End point title	Percentage of Subjects with Uric Acid Levels- ITT Population and PP Population[2]

End point description:

Analysis was performed on ITT and PP population.

End point type	Primary

End point timeframe:

28 days post treatment

Notes:

[2] - 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: Statistical analysis could not be provided due to EudraCT format constraint for single arm study.

End point values	Rasburicase			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: percentage of subjects				
number (not applicable)				
ITT Population: Under NRV (n=19)	10.5			
ITT Population: Normal (n=19)	36.8			
ITT Population: Upper NRV (n=19)	0			
ITT Population: Not Done (n=19)	52.6			
PP Population: Under NRV (n=18)	11.1			
PP Population: Normal (n=18)	38.9			
PP Population: Upper NRV (n=18)	0			
PP Population: Not Done (n=18)	50			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Creatinine Levels - ITT Population and PP Population

End point title	Percentage of Subjects with Creatinine Levels - ITT Population and PP Population

End point description:

Analysis was performed on ITT and PP population.

End point type	Secondary

End point timeframe:

24-48 hours

End point values	Rasburicase			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: percentage of subjects				
number (not applicable)				
ITT Population: Under NRV (n=21)	23.8			

ITT Population: Normal (n=21)	42.9			
ITT Population: Upper NRV (n=21)	19			
ITT Population: Not done (n=21)	14.3			
PP Population: Under NRV (n=20)	25			
PP Population: Normal (n=20)	40			
PP Population: Upper NRV (n=20)	20			
PP Population: Not done (n=20)	15			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Creatinine Levels - ITT Population and PP Population

End point title	Percentage of Subjects with Creatinine Levels - ITT Population and PP Population

End point description:

Analysis was performed on ITT and PP population.

End point type	Secondary

End point timeframe:

28 days post treatment

End point values	Rasburicase			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: percentage of subjects				
number (not applicable)				
ITT Population: Under NRV (n=19)	21.1			
ITT Population: Normal (n=19)	47.4			
ITT Population: Upper NRV (n=19)	5.3			
ITT Population: Not done (n=19)	26.3			
PP Population: Under NRV (n=18)	22.2			
PP Population: Normal (n=18)	44.4			
PP Population: Upper NRV (n=18)	5.6			
PP Population: Not done (n=18)	27.8			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All Adverse Events (AE) were collected from signature of the informed consent form up to the final visit (4 weeks after last medication dose) regardless of seriousness or relationship to investigational product.

Adverse event reporting additional description:

Reported adverse events and deaths are treatment-emergent that is AEs that developed/worsened and deaths that occurred during the 'time of first injection until last visit'. One death is not reported as subject did not receive any study medication.

Assessment type	Systematic

Dictionary used

Dictionary name	No Coding Applied
Dictionary version	0.0

Reporting groups

Reporting group title	Rasburicase

Reporting group description:

Rasburicase for 3 -7 days.

Serious adverse events	Rasburicase		
Total subjects affected by serious adverse events			
subjects affected / exposed	19 / 32 (59.38%)		
number of deaths (all causes)	5		
number of deaths resulting from adverse events			
General disorders and administration site conditions			
Diarrhea + Swelling			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	3 / 32 (9.38%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 2		
Sepsis + Pancytopenia			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia + Sara			

subjects affected / exposed	1 / 32 (3.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac congestive insufficiency				
subjects affected / exposed	1 / 32 (3.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal failure				
subjects affected / exposed	1 / 32 (3.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Bleeding				
subjects affected / exposed	1 / 32 (3.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Febrile neutropenia				
subjects affected / exposed	4 / 32 (12.50%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Diarrhea				
subjects affected / exposed	1 / 32 (3.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Fever				
subjects affected / exposed	2 / 32 (6.25%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Febrile granulocytopenia				
subjects affected / exposed	2 / 32 (6.25%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Seizure with transitory heparesis				

subjects affected / exposed	1 / 32 (3.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Seizure				
subjects affected / exposed	1 / 32 (3.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Epigastric pain				
subjects affected / exposed	1 / 32 (3.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Creatinin level increase				
subjects affected / exposed	1 / 32 (3.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Perianal hyperemia				
subjects affected / exposed	1 / 32 (3.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Central nervous system bleeding				
subjects affected / exposed	1 / 32 (3.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Oliguria + Hypovolemia + Cardiac congestive insufficiency + Acute lung edema				
subjects affected / exposed	1 / 32 (3.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			

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	23 / 32 (71.88%)		
General disorders and administration site conditions			
Febrile neutropenia			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		
Allergic reaction			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	3		
Ankle pain			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		
Vomiting			
subjects affected / exposed	11 / 32 (34.38%)		
occurrences (all)	16		
Nausea			
subjects affected / exposed	5 / 32 (15.63%)		
occurrences (all)	5		
Headache			
subjects affected / exposed	3 / 32 (9.38%)		
occurrences (all)	4		
Diarrhea			
subjects affected / exposed	4 / 32 (12.50%)		
occurrences (all)	4		
Hepatic enzymes increase			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		
Fever			
subjects affected / exposed	5 / 32 (15.63%)		
occurrences (all)	6		
Petechiase			
subjects affected / exposed	4 / 32 (12.50%)		
occurrences (all)	4		
Dry cough			

subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		
Epigastric pain			
subjects affected / exposed	4 / 32 (12.50%)		
occurrences (all)	4		
Emesis			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		
Lack of appetite			
subjects affected / exposed	3 / 32 (9.38%)		
occurrences (all)	3		
Mucositis			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		

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.

This study is considered as an "article 46" study by the EMA, although the completion date precedes 26 January 2007. Therefore this date was modified to allow posting.

Notes: