Clinical trial results:
Phase 2, Safety and Efficacy Study of Isatuximab, an Anti-CD38 Monoclonal Antibody, Administered by Intravenous (IV) Infusion in Patients with Relapsed or Refractory T-acute Lymphoblastic Leukemia (T-ALL) or T-lymphoblastic Lymphoma (T-LBL)

Summary

EudraCT number	2016-002739-14
Trial protocol	LT HU FI IT
Global end of trial date	14 November 2017

Results information

Result version number	v1 (current)
This version publication date	22 November 2018
First version publication date	22 November 2018

Trial information

Trial identification

Sponsor protocol code	ACT14596

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02999633
WHO universal trial number (UTN)	U1111-1179-5294

Notes:

Sponsors

Sponsor organisation name	Sanofi aventis recherche & développement
Sponsor organisation address	1 avenue Pierre Brossolette, Chilly- Mazarin, France,
Public contact	Sanofi aventis recherche & développement, Trial Transparency Team, US@sanofi.com
Scientific contact	Sanofi aventis recherche & développement, Trial Transparency Team, 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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	05 February 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 November 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of isatuximab in subjects with relapsed or refractory T-ALL or T-LBL as measured by overall response rate (ORR) (as per National Comprehensive Cancer Network [NCCN] guidelines).

Protection of trial subjects:

Subjects were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the subject and considering the local culture. During the course of the trial, subjects were provided with individual subject cards indicating the nature of the trial the subject is participating, contact details and any information needed in the event of a medical emergency. Collected personal data and human biological samples were processed in compliance with the Sanofi-Aventis Group Personal Data Protection Charter ensuring that the Group abides by the laws governing personal data protection in force in all countries in which it operates.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 March 2017
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	Finland: 1
Country: Number of subjects enrolled	France: 6
Country: Number of subjects enrolled	Lithuania: 1
Country: Number of subjects enrolled	Italy: 2
Country: Number of subjects enrolled	Russian Federation: 3
Country: Number of subjects enrolled	United States: 1
Worldwide total number of subjects	14
EEA total number of subjects	10

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)	0
Adolescents (12-17 years)	1
Adults (18-64 years)	10
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted in 6 countries. A total of 16 subjects were screened of those 2 subjects failed screening: 1 subject for evidence of ongoing infection and 1 subject for not meeting the criterion for relapsed or refractory T-acute lymphoblastic leukemia (ALL)/T-lymphoblastic lymphoma (LBL).

Pre-assignment

Screening details:

The first subject was enrolled on 14 March 2017. A total of 14 subjects were enrolled to receive isatuximab. The study was early terminated on 08 Nov 2017.

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	Isatuximab

Arm description:

Subjects received intravenous administration of isatuximab at a dose of 20 mg/kg at Day 1, 8, 15 and 22 of each Cycle (up to 2 treatment cycles, each cycle 28 days).

Arm type	Experimental
Investigational medicinal product name	Isatuximab
Investigational medicinal product code	SAR650984
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received intravenous administration of isatuximab at a dose of 20 milligram/kilogram (mg/kg).

Number of subjects in period 1	Isatuximab
Started	14
Completed	0
Not completed	14
Adverse Event	2
Progressive disease	12

Baseline characteristics

Reporting groups	
Reporting group title	Isatuximab
Reporting group description:	
Subjects received intravenous administration of isatuximab at a dose of 20 mg/kg at Day 1, 8, 15 and 22 of each Cycle (up to 2 treatment cycles, each cycle 28 days).	

Reporting group values	Isatuximab	Total	
Number of subjects	14	14	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 41.36 ± 19.30	 -	
Gender categorical Units: Subjects			
Female Male	2 12	2 12	

End points

End points reporting groups

Reporting group title	Isatuximab

Reporting group description:

Subjects received intravenous administration of isatuximab at a dose of 20 mg/kg at Day 1, 8, 15 and 22 of each Cycle (up to 2 treatment cycles, each cycle 28 days).

Primary: Percentage of Subjects With Objective Response

End point title	Percentage of Subjects With Objective Response[1]

End point description:

Objective response was defined as percentage of subjects with complete response or with complete response with incomplete peripheral recovery as per National Comprehensive Cancer Network (NCCN) guidelines. Complete response was defined as no circulating blasts or extramedullary disease, no lymphadenopathy, splenomegaly, skin/gum infiltration/testicular mass/central nervous system involvement, trilineage hematopoiesis and less than 5 percentage blasts, absolute neutrophil count (ANC) greater than 1000 per micro liter, platelets less than 100 000 per micro liter, no recurrence for 4 weeks. Complete response with incomplete blood count recovery (Cri) meet all criteria for complete response except platelet count and/or ANC. Safety analysis set included all subjects who received at least 1 dose of isatuximab.

End point type	Primary

End point timeframe:

Baseline until disease progression or death (maximum duration: 12.1 weeks)

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: Only descriptive data was planned to be analysed for this study.

End point values	Isatuximab			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: percentage of subjects				
number (confidence interval 95%)	0 (0 to 23.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR)

End point title	Duration of Response (DOR)

End point description:

DOR defined as time (in days) from date of first response until date of first documented progressive disease (PD) or death (from any cause), whichever came first. Progressive disease as per NCCN guidelines was defined as increase of at least 25% in the absolute number of circulating or bone marrow blasts or development of extramedullary disease. The endpoint was not analyzed due to lack of objective response. There was no specific additional data collected for the analysis of DOR as this endpoint was to be derived using time point responses and death information that were collected and analyzed as part of primary endpoint and safety endpoints, respectively.

End point type	Secondary

End point timeframe:

Baseline until disease progression or death (maximum duration: 12.1 weeks)

End point values	Isatuximab			
Subject group type	Reporting group			
Number of subjects analysed	0[2]			
Units: days				
number (not applicable)				

Notes:

[2] - The endpoint was not analyzed due to lack of objective response.

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)

End point description:

PFS was defined as the time interval (in days) from the date of first study drug administration to the date of first observation of PD or death due to any cause, whichever came first. PD as per NCCN guidelines was defined as increase of at least 25% in the absolute number of circulating or bone marrow blasts or development of extramedullary disease. The endpoint was not analyzed due to lack of objective response. There was no specific additional data collected for the analysis of PFS as this endpoint was to be derived using time point responses and death information that were collected and analyzed as part of primary endpoint and safety endpoints, respectively.

End point type	Secondary

End point timeframe:

Baseline until disease progression or death (maximum duration: 12.1 weeks)

End point values	Isatuximab			
Subject group type	Reporting group			
Number of subjects analysed	0[3]			
Units: days				
number (not applicable)				

Notes:

[3] - The endpoint was not analyzed due to lack of objective response.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

OS was defined as the time interval from the date of first study drug administration to the date of death due to any cause. The endpoint was not analyzed due to lack of objective response. There was no

specific additional data collected for the analysis of OS as this endpoint was to be derived using time point responses and death information that were collected and analyzed as part of primary endpoint and safety endpoints, respectively.

End point type	Secondary

End point timeframe:

Baseline until disease progression or death (maximum duration: 12.1 weeks)

End point values	Isatuximab			
Subject group type	Reporting group			
Number of subjects analysed	0[4]			
Units: days				
number (not applicable)				

Notes:

[4] - The endpoint was not analyzed due to lack of objective response.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Minimal Residual Disease (MRD)

End point title	Number of Subjects With Minimal Residual Disease (MRD)

End point description:

Presence of MRD was measured by sequencing and/or flow cytometry in subjects achieving CR and CRi. Complete response was defined as no circulating blasts or extramedullary disease, no lymphadenopathy, splenomegaly, skin/gum infiltration/testicular mass/central nervous system involvement, trilineage hematopoiesis and less than 5 percentage blasts, absolute neutrophil count (ANC) greater than 1000 per micro liter, platelets less than 100 000 per micro liter, no recurrence for 4 weeks. Complete response with incomplete blood count recovery (Cri) meet all criteria for complete response except platelet count and/or ANC. The endpoint was not analyzed because no subject achieved CR or CRi.

End point type	Secondary

End point timeframe:

Baseline until disease progression or death (maximum duration: 12.1 weeks)

End point values	Isatuximab			
Subject group type	Reporting group			
Number of subjects analysed	0[5]			
Units: subjects				

Notes:

[5] - The endpoint was not analyzed because no subject achieved CR or CRi.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to 30 days after last dose of study drug administration (up to maximum of 12.1 weeks)

Adverse event reporting additional description:

Reported Adverse events(AEs) are treatment emergent adverse events that is AEs that developed/worsened during the 'on treatment period' (from first study treatment administration until 30 days after the last administration of study treatment). Safety analysis set included all subjects who received at least 1 dose of isatuximab.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Isatuximab

Reporting group description:

Subjects received intravenous administration of isatuximab at a dose of 20 mg/kg at Day 1, 8, 15 and 22 of each Cycle (up to 2 treatment cycles, each cycle 28 days).

Serious adverse events	Isatuximab		
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 14 (71.43%)		
number of deaths (all causes)	6		
number of deaths resulting from adverse events	0		
Vascular disorders			
Pelvic Venous Thrombosis			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vein Collapse			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute Myocardial Infarction			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Pericarditis Constrictive			

subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Disease Progression			
subjects affected / exposed	4 / 14 (28.57%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 4		
Gastrointestinal disorders			
Pancreatitis			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Acute Respiratory Failure			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Pleural Effusion			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary Oedema			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Device Related Infection			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fungal Infection			

subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Periorbital Cellulitis			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	1 / 14 (7.14%)		
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	Isatuximab		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 14 (85.71%)		
Vascular disorders			
Phlebitis			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Pain			

subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	5 / 14 (35.71%)		
occurrences (all)	6		
Immune system disorders			
Cytokine Release Syndrome			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Bronchitis Chronic			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Bronchostenosis			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Cough			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	2		
Dysphonia			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Dyspnoea			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Haemoptysis			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Hypoxia			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Pharyngeal Erythema			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Pleural Effusion			

subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Productive Cough			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Respiratory Failure			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Wheezing			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Investigations			
Body Temperature Increased			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Weight Decreased			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Infusion Related Reaction			
subjects affected / exposed	8 / 14 (57.14%)		
occurrences (all)	11		
Cardiac disorders			
Tachycardia			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	2		
Nervous system disorders			
Facial Paralysis			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	2		
Peripheral Motor Neuropathy			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		

Sciatica subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Neutropenia subjects affected / exposed occurrences (all) Thrombocytopenia subjects affected / exposed occurrences (all)	 1 / 14 (7.14%) 1 1 / 14 (7.14%) 1 1 / 14 (7.14%) 2		
Gastrointestinal disorders Abdominal Pain Upper subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	 1 / 14 (7.14%) 1 2 / 14 (14.29%) 2 2 / 14 (14.29%) 2 1 / 14 (7.14%) 1 1 / 14 (7.14%) 1		
Hepatobiliary disorders Cholangitis subjects affected / exposed occurrences (all) Cholecystitis subjects affected / exposed occurrences (all)	 1 / 14 (7.14%) 1 1 / 14 (7.14%) 1		
Renal and urinary disorders			

Urinary Retention			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	2		
Bone Pain			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	2		
Flank Pain			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	2		
Muscle Oedema			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Musculoskeletal Pain			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Pain In Extremity			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Infections and infestations			
Bronchiolitis			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Device Related Infection			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Oral Herpes			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Pyelitis			

subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Rhinitis			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 February 2017	Following amendments were made: - Change contraception period from '2 weeks prior to screening' into '2 weeks prior to the first dose of isatuximab - Added blood typing and screen at screening - Removed mandatory chest X-ray from study time points other than screening period - Clarified the definition of Pharmacokinetic (PK) population - Clarified PK/PDy sampling time window and allowances - Reduced the number of PK samplings during the study - Added immunophenotyping sample collection during the induction period - Clarified the bone marrow sample collections and change sampling timing for receptor occupancy/receptor density - Editorial changes to improve clarity (add study name, abbreviations, grammatical corrections - Update of bioanalysis methods and locations for cytokines and markers of activated complements panel - Add interleukin (IL)-4 to the cytokine panel.

Notes:

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.

The study was stopped prior to the interim analysis due to lack of efficacy of isatuximab monotherapy for this study population. Therefore, majority of efficacy evaluations originally planned were no longer considered relevant and were not performed.

Notes: