Clinical trial results:
An Open-label, First-in-human, Dose Escalation Study of SAR440234 Administered as Single Agent by Intravenous Infusion in Patients with Relapsed or Refractory Acute Myeloid Leukemia (R/R AML), B-cell Acute Lymphoblastic Leukemia (B-ALL), or High Risk Myelodysplasia (HR-MDS)

Summary

EudraCT number	2017-004148-39
Trial protocol	FR
Global end of trial date	06 April 2021

Results information

Result version number	v1 (current)
This version publication date	22 April 2022
First version publication date	22 April 2022

Trial information

Trial identification

Sponsor protocol code	TED15138

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03594955
WHO universal trial number (UTN)	U1111-1197-8041

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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	27 May 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 April 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Dose Escalation Part: To determine the maximum tolerated dose (MTD)/maximum administered dose (MAD) of SAR440234 administered as a single agent in subjects with relapsed or refractory acute myeloid leukemia (R/R AML), high risk myelodysplasia (HR-MDS), or B-cell acute lymphoblastic leukemia (B-ALL) and determine the recommended Phase 2 dose (RP2D) for the subsequent Expansion Part. Expansion Part: To assess the activity of single agent SAR440234 at the RP2D in subjects with R/R AML or HR-MDS.

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	24 October 2018
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	United States: 2
Country: Number of subjects enrolled	France: 5
Worldwide total number of subjects	7
EEA total number of subjects	5

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)	0
Adults (18-64 years)	2
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study was conducted at 4 sites in France and the United States. A total of 12 subjects were screened, of whom 5 subjects were screen failures, mainly due to not meeting inclusion criteria. A total of 7 subjects were enrolled and treated in Dose Escalation Part before termination of study.

Pre-assignment

Screening details:

Study consisted of 2 parts: Dose Escalation and Expansion. Enrollment of subjects in Dose Expansion Part was planned to start after completion of Dose Escalation Part. Due to early termination of study, Dose Expansion Part was not conducted.

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	SAR440234

Arm description:

SAR440234 was administered as intravenous (IV) infusion once weekly for 6 weeks per Cycle. Per plan, subjects were to receive first 2 to 3 doses as Lead-in doses followed by a fixed dose until the end of treatment or unless the dose needs to be decreased for safety reasons. Due to early study termination, all subjects received only 1 treatment cycle at a dose of 1 nanogram per kilogram (ng/kg) once weekly.

Arm type	Experimental
Investigational medicinal product name	SAR440234
Investigational medicinal product code	SAR440234
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

SAR440234 IV infusion weekly for 6 weeks in Cycle 1. Dose escalation scheme was followed for first 3 weeks in Cycle 1 and then fixed doses were given from Week 4 to Week 6 unless the dose needed to be decreased for safety reasons.

Number of subjects in period 1	SAR440234
Started	7
Completed	0
Not completed	7
Sponsor's decision	1
Adverse event	1
Progressive disease	5

Baseline characteristics

Reporting groups	
Reporting group title	SAR440234

Reporting group description:

SAR440234 was administered as intravenous (IV) infusion once weekly for 6 weeks per Cycle. Per plan, subjects were to receive first 2 to 3 doses as Lead-in doses followed by a fixed dose until the end of treatment or unless the dose needs to be decreased for safety reasons. Due to early study termination, all subjects received only 1 treatment cycle at a dose of 1 nanogram per kilogram (ng/kg) once weekly.

Reporting group values	SAR440234	Total	
Number of subjects	7	7	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	68.0		
standard deviation	± 10.4	-	
Gender categorical Units: Subjects			
Male	3	3	
Female	4	4	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	0	0	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	0	0	
White	3	3	
More than one race	0	0	
Unknown or Not Reported	4	4	

End points

End points reporting groups

Reporting group title	SAR440234

Reporting group description:

SAR440234 was administered as intravenous (IV) infusion once weekly for 6 weeks per Cycle. Per plan, subjects were to receive first 2 to 3 doses as Lead-in doses followed by a fixed dose until the end of treatment or unless the dose needs to be decreased for safety reasons. Due to early study termination, all subjects received only 1 treatment cycle at a dose of 1 nanogram per kilogram (ng/kg) once weekly.

Primary: Dose Escalation Part: Number of Subjects With Dose Limiting Toxicities (DLTs)

End point title	Dose Escalation Part: Number of Subjects With Dose Limiting Toxicities (DLTs)[1]

End point description:

DLTs: occurrence of any of following related to investigational medicinal product (IMP): Any grade (G) greater than or equal to (>=) 3 nonhematological adverse events (AE); G4 hematological toxicities (bone marrow hypocellularity, decreased neutrophils, febrile neutropenia, decreased platelet count and anemia) as defined in national cancer institute common terminology criteria for adverse events (NCI-CTCAE, v4.03); G3/G4 cytokine release syndrome (CRS) (G1: fever, nausea, fatigue, headache, myalgias and malaise; G2: oxygen requirement less than[<] 40 percent (%); G3: oxygen requirement greater than[>] 40% ; G4: life-threatening symptoms, requirement for mechanical ventilation, organ toxicity, G5:death) graded by NCI Consensus Guidelines; Grade 2 CRS for >48 hours/<48 hours before IMP; any treatment-emergent AE of potential significance and IMP-related adverse reaction lasted >2 weeks with failure to recover to baseline/improve to G less than or equal to(<=1). DLT evaluable population.

End point type	Primary

End point timeframe:

Cycle 1 (42 days)

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

End point values	SAR440234			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: subjects	1			

Statistical analyses

No statistical analyses for this end point

Primary: Dose Escalation Part: Number of Subjects With Allergic Reactions/Hypersensitivity and Cytokine Release Syndrome/Acute Infusion Reactions

End point title	Dose Escalation Part: Number of Subjects With Allergic Reactions/Hypersensitivity and Cytokine Release Syndrome/Acute Infusion Reactions[2]

End point description:

In this endpoint, number of subjects with allergic reactions or hypersensitivity and CRS or acute infusion

reactions is reported. CRS is a nonantigen specific toxicity that occurs as result of potent immune activation mediated by large, rapid release of cytokines into blood from immune cells affected by IMP. Grading and management of CRS was based on National Cancer Institute (NCI) Consensus Guidelines 2014. Allergic/Hypersensitivity reactions or acute infusion reactions are defined as disorder characterised by adverse local/general response from exposure to allergen; graded by NCI CTCAE v4.03. Analysis was performed on safety population which included all registered subjects who had given their informed consent and had received at least 1 dose of SAR440234. Analysis was performed on safety population which included all registered subjects who had given their informed consent and had received at least 1 dose of SAR440234.

End point type	Primary

End point timeframe:

First IMP administration (Day 1) up to last dose of IMP + 30 days (i.e., up to 72 days)

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

End point values	SAR440234			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: subjects	2			

Statistical analyses

No statistical analyses for this end point

Primary: Expansion Part: Percentage of Subjects With Overall Response (OR) Per International Working Group (IWG) Criteria

End point title	Expansion Part: Percentage of Subjects With Overall Response (OR) Per International Working Group (IWG) Criteria[3]

End point description:

Response: assessed by IWG 2003 recommendations for acute myeloid leukemia (AML) and revised 2000 criteria for myelodysplastic syndrome (MDS). MDS - OR: complete remission (CR)/marrow CR/partial remission (PR), CR: repeat bone marrow show <5% myeloblasts and peripheral blood evaluations lasting >=2 months hemoglobin (>11 grams per decilitre), neutrophils 1500 per cubic millimetre (mm^3), platelets >=100000/mm^3, blasts 0% and no dysplasia, PR: all CR criteria except blasts decreased by >=50% over pretreatment or less advanced than pretreatment. AML - OR:CR/CR with incomplete hematological recovery(CRi)/PR, CR:absolute neutrophil count (ANC) >=1000 per microliter (mcL), platelets >=100000/mcL, <5% blast cells in bone marrow; auer rods should not be detectable; no platelet/whole blood transfusions for 7 days prior hematology test. CRi:all criteria of CR except platelets and/or ANC. PR:all CR criteria except blasts decreased by >=50% over pretreatment or less advanced than pretreatment.

End point type	Primary

End point timeframe:

From the date of first IMP administration until disease progression or death, whichever came earlier (up to 42 days)

Notes:

[3] - 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: As the endpoint was descriptive in nature, no statistical analysis was provided.

End point values	SAR440234			
Subject group type	Reporting group			
Number of subjects analysed	0[4]			
Units: percentage of subjects				
number (not applicable)				

Notes:

[4] - Due to the early termination of the study, data for this endpoint was not collected and analysed.

Statistical analyses

No statistical analyses for this end point

Primary: Expansion Part: Duration of Response (DOR)

End point title	Expansion Part: Duration of Response (DOR)[5]

End point description:

DOR: time from first tumor assessment at which the overall response was recorded as CR, marrow CR, or PR (MDS) and CR/CRi (AML) until documented progressive disease (PD) determined by IWG criteria, or death from any cause, whichever occurred first. Per IWG criteria, relapse was defined as reappearance of blasts in blood or bone marrow (>5%) or in any extramedullary site after a CR. CR:<= 5% myeloblasts in bone marrow with no evidence of persistent dysplasia; peripheral blood showing hemoglobin>=11g/dL. Marrow CR: no circulating blasts, <5% blast, absolute neutrophil count >1000/mcL, platelets >100000/mcL, no recurrence for 4 weeks. CRi: meet all criteria for CR except platelet count and/or ANC. PR: all CR criteria except blasts decreased by >=50% over pretreatment or less advanced than pretreatment. Progression: at least 50% decrease from maximum remission/response in granulocytes/platelets; reduction in Hgb by >=2 g/dL; transfusion dependence.

End point type	Primary

End point timeframe:

From 1st documentation of response to date of first documentation of disease progression or death, whichever came earlier (up to 42 days)

Notes:

[5] - 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: As the endpoint was descriptive in nature, no statistical analysis was provided.

End point values	SAR440234			
Subject group type	Reporting group			
Number of subjects analysed	0[6]			
Units: days				
arithmetic mean (standard deviation)	()			

Notes:

[6] - Due to the early termination of the study, data for this endpoint was not collected and analysed.

Statistical analyses

No statistical analyses for this end point

Primary: Expansion Part: Number of Subjects With Disease-free Survival

End point title	Expansion Part: Number of Subjects With Disease-free

End point description:

Disease-free survival was defined as the time from date of first administration of study intervention until the earliest of any of the following: date of death or date of first response assessment confirming relapse or date of final response assessment which fails to confirm response whichever occurred first.

End point type	Primary

End point timeframe:

First IMP administration to date of first documentation of disease progression or relapse or death, whichever came earlier (up to 42 days)

Notes:

[7] - 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: As the endpoint was descriptive in nature, no statistical analysis was provided.

End point values	SAR440234			
Subject group type	Reporting group			
Number of subjects analysed	0[8]			
Units: subjects				

Notes:

[8] - Due to the early termination of the study, data for this endpoint was not collected and analysed.

Statistical analyses

No statistical analyses for this end point

Secondary: Dose Escalation Part: Number of Subjects With Treatment-emergent Adverse Events (TEAEs) and Treatment-emergent Serious Adverse Events (TESAEs)

End point title	Dose Escalation Part: Number of Subjects With Treatment-emergent Adverse Events (TEAEs) and Treatment-emergent Serious Adverse Events (TESAEs)

End point description:

An AE was defined as any untoward medical occurrence in a subject who received study drug and did not necessarily had to have a causal relationship with the treatment. Serious AEs (SAEs) were any untoward medical occurrence that resulted in any of the following outcomes: death, life-threatening, required initial or prolonged in-patient hospitalisation, persistent or significant disability/incapacity, congenital anomaly/birth defect, or considered as medically important event. TEAEs were defined as the AEs that developed or worsened or became serious during the TEAE period (defined as the time from the first dose of the IMP to the last dose of IMP + 30 days). Analysis was performed on safety population.

End point type	Secondary

End point timeframe:

From Baseline (Day 1) up to last dose of IMP + 30 days (i.e., up to 72 days)

End point values	SAR440234			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: subjects				
Any TEAE	7			
Any TESAE	6			

Statistical analyses

No statistical analyses for this end point

Secondary: Dose Escalation Part: Percentage of Subjects With Objective Response Per IWG Criteria

End point title	Dose Escalation Part: Percentage of Subjects With Objective Response Per IWG Criteria

End point description:

Objective response was defined as the percentage of subjects who had a marrow CR, or PR (MDS) and CR/CRi (AML) per IWG criteria. For MDS, CR: repeat bone marrow show <5% myeloblasts and peripheral blood evaluations lasting >=2 months of hemoglobin (>11 g/dL), neutrophils 1500/mm^3, platelets >=100000/mm^3, blasts 0% and no dysplasia, PR: all CR criteria except blasts decreased by >=50% over pretreatment or less advanced than pretreatment. For AML, CR: ANC >=1000/mcL, platelet count >=100000/mcL, bone marrow should contain <5% blast cells; auer rods should not be detectable; no platelet/whole blood transfusions for 7 days prior to date of hematology assessment. CRi: morphologic complete remission but ANC count might be <1000/mcL or platelet <100000/mcL.

End point type	Secondary

End point timeframe:

From the date of first IMP administration until disease progression or death, whichever came earlier (up to 42 days)

End point values	SAR440234			
Subject group type	Reporting group			
Number of subjects analysed	0[9]			
Units: percentage of subjects				
number (not applicable)				

Notes:

[9] - Due to the early termination of the study, data for this endpoint was not collected and analysed.

Statistical analyses

No statistical analyses for this end point

Secondary: Immunogenicity: Number of Subjects With Treatment-Emergent Anti-drug Antibodies (ADA) Response

End point title	Immunogenicity: Number of Subjects With Treatment-Emergent Anti-drug Antibodies (ADA) Response

End point description:

ADA response categories: 1) Treatment-induced ADA: subjects without pre-existing ADA and without pretreatment samples and who developed ADAs during the TEAE period. 2) Treatment-boosted ADA: subjects with pre-existing ADAs that was increased at least a 4-fold in titer compared to Baseline during the TEAE period. 2) Treatment-emergent ADA: subjects with at least one treatment-induced/boosted ADA sample. TEAE period was defined as the time from the first dose of the IMP to the last dose of the IMP + 30 days. Analysis was performed on ADA population which included all subjects who had given their informed consent, had received at least 1 dose (even incomplete) of SAR440234 and had at least 1 available ADA result after IMP administration.

End point type	Secondary

End point timeframe:

From Baseline (Day 1) up to last dose of IMP + 30 days (i.e., up to 72 days)

End point values	SAR440234			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: subjects	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics (PK): Maximum Observed Plasma Concentration (Cmax) of SAR440234

End point title	Pharmacokinetics (PK): Maximum Observed Plasma Concentration (Cmax) of SAR440234

End point description:

Cmax was the maximum observed plasma concentration. Cmax was obtained by a non-compartmental analysis. Here in the time frame, Day = D, start of infusion = SOI, mid of infusion = MOI, end of infusion = EOI and hours = H. Analysed on PK population which included subjects who had given their informed consent and had received at least one dose (even incomplete) of SAR440234 with at least 1 evaluable drug concentration after IMP administration. Here, 'n' = subjects with available data for each specified category, '99999' indicates that mean and standard deviation (SD) were not estimable as no subject had plasma concentration greater than lower limit of quantification and '9999' indicates that SD was not estimable because only 1 subject was available for the analysis at the specified time point.

End point type	Secondary

End point timeframe:

Cycle 1: D 1: SOI, EOI, 1, 2, 5, 7, 24, 48, 72 H post EOI; D 8: SOI, MOI, EOI, 2, 5, 168 H post EOI; D 15: MOI, EOI, 2, 5, 24 H post EOI; D 22: SOI, MOI, EOI, 2, 5, 24, 48, 72, 96, 168 H post EOI; D 29: EOI, 2 H post EOI; D 36: SOI, EOI, 2 H post EOI

End point values	SAR440234			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: picograms per milliliter				
arithmetic mean (standard deviation)				
Cycle 1 day 1 (n = 7)	64.7 (± 171)			
Cycle 1 day 8 (n = 7)	99999 (± 99999)			
Cycle 1 day 15 (n = 5)	99.1 (± 115)			
Cycle 1 day 22 (n = 5)	57.1 (± 22.6)			
Cycle 1 day 29 (n = 3)	74.5 (± 90.3)			
Cycle 1 day 36 (n = 1)	70.4 (± 9999)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of IMP up to 30 days after the last dose of IMP (i.e., up to 72 days)

Adverse event reporting additional description:

Reported AEs and deaths were TEAEs that developed/worsened in grade or became serious during TEAE period (defined as the time from the first dose of the IMP to the last dose of IMP + 30 days). Analysis was performed on safety population.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	SAR440234

Reporting group description:

SAR440234 was administered as intravenous (IV) infusion once weekly for 6 weeks per Cycle. Per plan, subjects were to receive first 2 to 3 doses as Lead-in doses followed by a fixed dose until the end of treatment or unless the dose needs to be decreased for safety reasons. Due to early study termination, all subjects received only 1 treatment cycle at a dose of 1 nanogram per kilogram (ng/kg) once weekly.

Serious adverse events	SAR440234		
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 7 (100.00%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events			
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile Neutropenia			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Thrombocytopenia			
subjects affected / exposed	1 / 7 (14.29%)		
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	3 / 7 (42.86%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 3		
Pyrexia			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Cytokine release syndrome			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Perirectal abscess			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia moraxella			

subjects affected / exposed	1 / 7 (14.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	SAR440234		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 7 (100.00%)		
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Deep vein thrombosis			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	3 / 7 (42.86%)		
occurrences (all)	3		
Chills			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Oedema peripheral			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Gait disturbance			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	2 / 7 (28.57%)		
occurrences (all)	5		
Tenderness			

subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Immune system disorders			
Cytokine release syndrome			
subjects affected / exposed	2 / 7 (28.57%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Epistaxis			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Pulmonary Mass			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Investigations			
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Alanine aminotransferase increased			
subjects affected / exposed	2 / 7 (28.57%)		
occurrences (all)	2		
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 7 (28.57%)		
occurrences (all)	2		
Headache			

subjects affected / exposed occurrences (all)	2 / 7 (28.57%) 5		
Blood and lymphatic system disorders Febrile neutropenia subjects affected / exposed occurrences (all) Thrombocytopenia subjects affected / exposed occurrences (all) Pancytopenia subjects affected / exposed occurrences (all)	 1 / 7 (14.29%) 1 1 / 7 (14.29%) 2 1 / 7 (14.29%) 1		
Ear and labyrinth disorders Deafness subjects affected / exposed occurrences (all)	 1 / 7 (14.29%) 1		
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all) Gastrointestinal haemorrhage subjects affected / exposed occurrences (all) Gingival bleeding subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Gingival Hypertrophy subjects affected / exposed occurrences (all) Nausea	 3 / 7 (42.86%) 3 2 / 7 (28.57%) 3 1 / 7 (14.29%) 1 1 / 7 (14.29%) 1 1 / 7 (14.29%) 1 1 / 7 (14.29%) 1 		

subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1		
Oral disorder subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 2		
Odynophagia subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1		
Proctalgia subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1		
Skin and subcutaneous tissue disorders			
Dry Skin subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1		
Pruritus subjects affected / exposed occurrences (all)	2 / 7 (28.57%) 3		
Erythema subjects affected / exposed occurrences (all)	2 / 7 (28.57%) 4		
Ecchymosis subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 2		
Purpura subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1		
Renal and urinary disorders			
Micturition urgency subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1		
Musculoskeletal and connective tissue disorders			
Bone Pain subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1		
Pain in extremity			

subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Back Pain			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Infections and infestations			
Urinary Tract Infection			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Staphylococcal Bacteraemia			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Oral Candidiasis			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Hypertriglyceridaemia			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Hypo Hdl Cholesterolaemia			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Hypocalcaemia			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Hypophosphataemia			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 May 2018	Following changes were made: Clarify some discontinuation criteria; Modify some Inclusion/Exclusion criteria; Define overdose for oral intake; Update premedication prior to infusion. Additional premedication is now required: dexamethasone 20 mg IV and montelukast 10 mg oral (PO) 4 hours prior to the start of SAR440234; Update dose modification rules for Grade 3 and 4 CRS; Add specific guidelines for the risk stratification, diagnosis, prevention, and treatment of tumor lysis syndrome; Add magnesium to blood chemistry.
15 February 2019	The following changes were made: - Updated exclusion criteria - Modify allowed chemotherapy to permit use of hydroxyurea, if needed, to control the white blood count during Cycle 1. - Clarified wording in the dose delay/reduction section to avoid misinterpretations. - Clarified wording of DLT definitions. - Updated flow charts section with below details. - Require performance of Day 42 assessment on the day that the subject discontinues therapy with SAR440234. - Require performance of end of treatment (EOT) assessment within 30 days of last SAR440234 administration. - Require follow up via telephone call and record review if a subject was unable to return to clinic for monthly study visits after discontinuing SAR440234. - Clarified enrollment schedule and some discontinuation criteria. - Modified some Inclusion/Exclusion criteria. - Defined overdose of oral intake. - Updated premedication prior to infusion: Additional premedication is now required: dexamethasone 20 mg IV and monteleukast 10 mg oral (PO) 4 hours prior to the start of SAR440234. - Updated dose modification rules for Grade 3 and 4 CRS. - Added specific guidelines for the risk stratification, diagnosis, prevention, and treatment of tumor lysis syndrome. - Added magnesium to blood chemistry.
29 August 2019	The following changes were made: - Text was added to clarify that the first 3 subjects treated during the Dose Escalation Part were replaced because abnormalities were detected in their PK profiles. These findings suggested that these subjects might had received unintentional overdoses of SAR440234 on some occasions. Data from these subjects would be used as part of the safety database but would not be used for dose escalation decision. - Clarified to be consistent with Clinical Trial Summary. - To improve the ability to detect safety signals accurately, the Dose Escalation Part will now follow a 3+3 trial design, rather than an accelerated design. - Text was added to draw attention to the importance of referring to the Pharmacy Manual regarding details of SAR440234 preparation and administration. - Correction of formatting, typographical errors and standardisation of wording to increase clarity.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
06 April 2021	Sponsor decision.	-

Notes:

Limitations and caveats

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

Sponsor decided to prioritise development of other novel therapies with more innovative mechanisms of action for R/R AML and other cancers. Thus, decided to terminate the study and stopped enrollment in Dose Expansion Part.

Notes: