Clinical trial results:
A Phase 2 Proof-of-Concept Study to Separately Evaluate the Activity of Talacotuzumab (JNJ-56022473) or Daratumumab in Transfusion-Dependent Subjects with Low or Intermediate-1 Risk Myelodysplastic Syndromes (MDS) who are Relapsed or Refractory to Erythropoiesis-Stimulating Agent (ESA) Treatment

Summary

EudraCT number	2016-003328-22
Trial protocol	BE NL ES IT
Global end of trial date	23 January 2019

Results information

Result version number	v1 (current)
This version publication date	14 October 2022
First version publication date	14 October 2022

Trial information

Trial identification

Sponsor protocol code	56022473MDS2002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03011034
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Janssen Research & Development, LLC
Sponsor organisation address	920 US Highway 202, Raritan, NJ, United States, 08869-1420
Public contact	Clinical Registry Group, Janssen Research & Development, LLC, ClinicalTrialsEU@its.jnj.com
Scientific contact	Clinical Registry Group, Janssen Research & Development, LLC, ClinicalTrialsEU@its.jnj.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	23 January 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 January 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial was to evaluate the efficacy (transfusion independence [TI]) of daratumumab in red blood cell (RBC) transfusion-dependent subjects with low or intermediate-1-risk myelodysplastic syndromes (MDS) whose disease had relapsed during treatment with or was refractory to erythropoiesis-stimulating agents (ESAs) (after enrollment in the talacotuzumab arm was stopped).

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the declaration of helsinki and that are consistent with Good Clinical Practices and applicable regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 March 2017
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	1 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 7
Country: Number of subjects enrolled	Spain: 10
Country: Number of subjects enrolled	Italy: 3
Country: Number of subjects enrolled	Netherlands: 3
Country: Number of subjects enrolled	Russian Federation: 3
Country: Number of subjects enrolled	United States: 8
Worldwide total number of subjects	34
EEA total number of subjects	23

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)	6
From 65 to 84 years	28
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Out of 34 enrolled subjects, 33 subjects received daratumumab and 1 subject received talacotuzumab. Due to serious infusion-related reaction (IRR) event that occurred in first subject enrolled in talacotuzumab arm, no further subjects were enrolled and no primary assessments were conducted for the single subject assigned to talacotuzumab arm.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Talacotuzumab

Arm description:

Subjects received a single dose of talacotuzumab 9 milligram per kilogram (mg/kg) intravenously (IV) every two weeks.

Arm type	Experimental
Investigational medicinal product name	Talacotuzumab
Investigational medicinal product code	
Other name	JNJ-56022473
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Talacotuzumab 9 mg/kg was administered intravenously (IV) as a single dose every two weeks.

Arm title	Daratumumab

Arm description:

Subjects received daratumumab 16 mg/kg IV weekly on Weeks 1 to 8 (on Days 1, 8, 15, and 22 of Cycles 1 and 2), every 2 weeks from Weeks 9 to 24 (on Days 1 and 15 of Cycles 3 to 6), and every 4 weeks thereafter (on Day 1 for all subsequent cycles). Each treatment cycle was of 28 days.

Arm type	Experimental
Investigational medicinal product name	Daratumumab
Investigational medicinal product code	
Other name	JNJ-54767414
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Daratumumab 16 mg/kg was administered IV weekly on Weeks 1 to 8 (on Days 1, 8, 15, and 22 of Cycles 1 and 2), every 2 weeks from Weeks 9 to 24 (on Days 1 and 15 of Cycles 3 to 6), and every 4 weeks thereafter (on Day 1 for all subsequent cycles).

Number of subjects in period 1	Talacotuzumab	Daratumumab
Started	1	33
Completed	0	33
Not completed	1	0
Adverse event, non-fatal	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Talacotuzumab
Reporting group description:	
Subjects received a single dose of talacotuzumab 9 milligram per kilogram (mg/kg) intravenously (IV) every two weeks.	
Reporting group title	Daratumumab
Reporting group description:	
Subjects received daratumumab 16 mg/kg IV weekly on Weeks 1 to 8 (on Days 1, 8, 15, and 22 of Cycles 1 and 2), every 2 weeks from Weeks 9 to 24 (on Days 1 and 15 of Cycles 3 to 6), and every 4 weeks thereafter (on Day 1 for all subsequent cycles). Each treatment cycle was of 28 days.	

Reporting group values	Talacotuzumab	Daratumumab	Total
Number of subjects	1	33	34
Title for AgeCategorical			
Units: subjects			
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	6	6
From 65 to 84 years	1	27	28
85 years and over	0	0	0
Title for AgeContinuous			
Units: years			
arithmetic mean	67	71.5	
standard deviation	± 99999	± 6.86	-
Title for Gender			
Units: subjects			
Female	0	8	8
Male	1	25	26

End points

End points reporting groups

Reporting group title	Talacotuzumab

Reporting group description:

Subjects received a single dose of talacotuzumab 9 milligram per kilogram (mg/kg) intravenously (IV) every two weeks.

Reporting group title	Daratumumab

Reporting group description:

Subjects received daratumumab 16 mg/kg IV weekly on Weeks 1 to 8 (on Days 1, 8, 15, and 22 of Cycles 1 and 2), every 2 weeks from Weeks 9 to 24 (on Days 1 and 15 of Cycles 3 to 6), and every 4 weeks thereafter (on Day 1 for all subsequent cycles). Each treatment cycle was of 28 days.

Primary: Percentage of Subjects who Achieved Red Blood Cell (RBC) Transfusion Independence (TI) Lasting at least 8 weeks

End point title	Percentage of Subjects who Achieved Red Blood Cell (RBC) Transfusion Independence (TI) Lasting at least 8 weeks[1][2]

End point description:

Percentage of subjects who achieved RBC TI lasting at least 8 weeks were reported. The 8-week RBC TI rate is defined as the percentage of subjects without any RBC transfusion during any consecutive 8 weeks (56 days) post randomization. Intent-to-treat (ITT) population included all subjects who received at least 1 dose of daratumumab.

End point type	Primary

End point timeframe:

Up to 2 years

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: No inferential statistics was planned for this primary endpoint.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was analysed for the specified arm only as no primary assessments were conducted for other arm.

End point values	Daratumumab			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: percentage of subjects				
number (confidence interval 95%)	6.1 (0.7 to 20.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Transfusion Independence (TI)

End point title	Time to Transfusion Independence (TI)[3]

End point description:

Time to transfusion independence (TI) was defined as time to the start of the TI interval. Pertaining only to subjects who achieved TI, time to the 8-week or 24-week RBC TI is defined as the interval from study

Day 1 to the first day of the first 8-week or 24-week RBC TI period. ITT population who achieved TI for at least 8 weeks. As less number of subjects were evaluable for this endpoint, the results were not summarized. Hence, subject wise data is reported. Here, N (number of subjects analysed) indicates number of subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Up to 2 years

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was analysed for the specified arm only as no primary assessments were conducted for other arm.

End point values	Daratumumab			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: weeks				
Subject 1	4			
Subject 2	5			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects who Achieved Red Blood Cell (RBC) Transfusion Independence (TI) Lasting at Least 24 Weeks

End point title	Percentage of Subjects who Achieved Red Blood Cell (RBC) Transfusion Independence (TI) Lasting at Least 24 Weeks[4]

End point description:

Percentage of subjects who achieved RBC TI lasting at least 24 weeks were reported. 24-week RBC TI rate is defined as the percentage of subjects without any RBC transfusion during any consecutive 24 weeks (168 days) post randomisation. ITT population included all subjects who received at least 1 dose of daratumumab.

End point type	Secondary

End point timeframe:

Up to 2 years

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was analysed for the specified arm only as no primary assessments were conducted for other arm.

End point values	Daratumumab			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: percentage of subjects				
number (confidence interval 95%)	3.0 (0.1 to 15.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Transfusion Independence (TI)

End point title	Duration of Transfusion Independence (TI)[5]

End point description:

Duration of TI was reported. Pertaining only to subjects who achieved TI, time to the 8-week or 24-week RBC TI is defined as the interval from Study Day 1 to the first day of the first 8-week or 24-week RBC TI period. ITT population who achieved TI for at least 8 weeks. As less number of subjects were evaluable for this outcome measure (OM), the results were not summarized. Hence, subject wise data is reported. Here, N (number of subjects analysed) indicates number of subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Up to 2 years

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint was analysed for the specified arm only as no primary assessments were conducted for other arm.

End point values	Daratumumab			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: weeks				
Subject 1	16			
Subject 2	65			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects who met International Working Group (IWG) Criteria for Transfusion Reduction

End point title	Percentage of Subjects who met International Working Group (IWG) Criteria for Transfusion Reduction[6]

End point description:

Percentage of subjects who met IWG criteria for transfusion reduction were reported. IWG criteria for transfusion reduction: at least 4 units reduction in RBC transfusions in the best 8-week interval. The best 8-week interval was a post-baseline 8-week interval where the subject had the fewest post-baseline RBC transfusion units. ITT population included all subjects who received at least 1 dose of daratumumab.

End point type	Secondary

End point timeframe:

Up to 2 years

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint was analysed for the specified arm only as no primary assessments were conducted for other arm.

End point values	Daratumumab			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: percentage of subjects				
number (not applicable)	54.5			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with at Least one Dose of Myeloid Growth Factors Usage

End point title	Percentage of Subjects with at Least one Dose of Myeloid Growth Factors Usage[7]

End point description:

Percentage of subjects with Myeloid Growth Factors (MGF) usage (who had used at least 1 dose of MGF) were reported. ITT population included all subjects who received at least 1 dose of daratumumab.

End point type	Secondary

End point timeframe:

Up to 2 years

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was analysed for the specified arm only as no primary assessments were conducted for other arm.

End point values	Daratumumab			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: percentage of subjects				
number (not applicable)	9.1			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Hematologic Improvement (HI) per IWG 2006 by Investigator Assessment

End point title	Percentage of Subjects with Hematologic Improvement (HI) per IWG 2006 by Investigator Assessment[8]

End point description:

Percentage of subjects with HI per IWG 2006 by investigator assessment were reported. Response criteria per IWG 2006 for HI: erythroid response (pretreatment, less than [<] 11 gram per deciliter [g/dL]) - hemoglobin (Hb) increase by greater than or equal to (>=) 1.5 g/dL, relevant reduction of units of RBC transfusions by an absolute number of at least 4 RBC transfusions/8 weeks compared with the pretreatment transfusion number in the previous 8 weeks. Only RBC transfusions given for a Hb of less than or equal to (<=) 9 g/dL pretreatment counted in the RBC transfusion response evaluation; platelet response (pretreatment, <100*10^9/L) - absolute increase of >=30*10^9/L for subjects starting with >20*10^9/L platelets. Increase from <20*10^9/L to >20*10^9/L and by at least 100 percent (%); neutrophil response (pretreatment, <1*10^9/L) - at least 100% increase and an absolute increase >0.5*10^9/L. ITT population included all subjects who received at least 1 dose of

daratumumab.

End point type	Secondary

End point timeframe:

Up to 2 years

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was analysed for the specified arm only as no primary assessments were conducted for other arm.

End point values	Daratumumab			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: percentage of subjects				
number (confidence interval 95%)				
Erythroid Response	9.1 (1.9 to 24.3)			
Platelet Response	0.0 (0.0 to 10.6)			
Neutrophil Response	0.0 (0.0 to 10.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Complete Remission (CR) and Marrow CR

End point title	Percentage of Subjects with Complete Remission (CR) and Marrow CR[9]

End point description:

Percentage of subjects with CR and marrow CR were reported. CR per IWG 2006 response criteria: bone marrow <= 5% myeloblasts with normal maturation of all cell lines, persistent dysplasia noted; peripheral blood - hemoglobin >=11 g/dL; platelets >=100*10^9/L; neutrophils >=1.0*10^9/L; blasts, 0%. Marrow CR: Bone marrow <=5% myeloblasts and decrease by >=50% over pretreatment; peripheral blood - if HI responses, they were noted in addition to marrow CR. ITT population included all subjects who received at least 1 dose of daratumumab.

End point type	Secondary

End point timeframe:

Up to 2 years

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was analysed for the specified arm only as no primary assessments were conducted for other arm.

End point values	Daratumumab			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: percentage of subjects				
number (not applicable)				
CR	0			
Marrow CR	3.0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Cytogenetic Response

End point title	Percentage of Subjects with Cytogenetic Response[10]

End point description:

Percentage of subjects with cytogenetic response were reported. Cytogenetic response per IWG 2006 response criteria: complete - disappearance of the chromosomal abnormality without appearance of new ones; partial - at least 50% reduction of the chromosomal abnormality. As there were no subjects who had the del(5q) abnormality at baseline, this assessment was not performed. ITT population included all participants who received at least 1 dose of daratumumab.

End point type	Secondary

End point timeframe:

Up to 2 years

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was analysed for the specified arm only as no primary assessments were conducted for other arm.

End point values	Daratumumab			
Subject group type	Reporting group			
Number of subjects analysed	0[11]			
Units: percentage of subjects				

Notes:

[11] - There were no subjects who had del(5q) abnormality at baseline, this assessment was not performed.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Partial Remission (PR)

End point title	Percentage of Subjects with Partial Remission (PR)[12]

End point description:

Percentage of subjects with PR were reported. PR per IWG 2006 response criteria: all CR criteria if abnormal before treatment except: bone marrow blasts decreased by >=50% over pretreatment but still >5%, cellularity and morphology not relevant. ITT population included all subjects who received at least 1 dose of daratumumab.

End point type	Secondary

End point timeframe:

Up to 2 years

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was analysed for the specified arm only as no primary assessments were

conducted for other arm.

End point values	Daratumumab			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: percentage of subjects	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Progression to Acute Myeloid Leukemia (AML)

End point title	Time to Progression to Acute Myeloid Leukemia (AML)[13]

End point description:

Time to progression to AML was reported. Time to progression to AML is defined as the interval from study Day 1 to the date of AML progression (bone marrow or peripheral blood blasts ≥20%). Disease progression as per IWG response criteria: for subjects with: <5% blasts: >=50% increase in blasts to >5% blasts; 5%–10% blasts: >=50% increase to >10% blasts; 10%–20% blasts: >=50% increase to >20% blasts; 20%–30% blasts: >=50% increase to >30% blasts. Any of the following: >=50% decrement from maximum remission/response in granulocytes or platelets; reduction in hemoglobin by >=2 g/dL; transfusion dependence. ITT population included all subjects who received at least 1 dose of daratumumab. Here, "99999" signifies that the median, lower and upper limit of Confidence Interval (CI) were not estimable due to lesser number of events.

End point type	Secondary

End point timeframe:

Up to 2 years

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was analysed for the specified arm only as no primary assessments were conducted for other arm.

End point values	Daratumumab			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: weeks				
median (confidence interval 95%)	99999 (54.7 to 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival[14]

End point description:

The overall survival was defined as the time from the date of first dose of study drug to date of death

from any cause. Median overall survival was estimated by using the Kaplan-Meier method. ITT population included all subjects who received at least 1 dose of daratumumab. Here, "99999" signifies that the median, lower and upper limit of Confidence Interval (CI) were not estimable due to lesser number of events.

End point type	Secondary

End point timeframe:

Up to 2 years

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was analysed for the specified arm only as no primary assessments were conducted for other arm.

End point values	Daratumumab			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 2 years

Adverse event reporting additional description:

The safety analysis set included all subjects who received at least one dose of study drug (daratumumab/ talacotuzumab).

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	Daratumumab

Reporting group description:

Subjects received daratumumab 16 mg/kg IV weekly on Weeks 1 to 8 (on Days 1, 8, 15, and 22 of Cycles 1 and 2), every 2 weeks from Weeks 9 to 24 (on Days 1 and 15 of Cycles 3 to 6), and every 4 weeks thereafter (on Day 1 for all subsequent cycles). Each treatment cycle was of 28 days.

Reporting group title	Talacotuzumab

Reporting group description:

Subjects received a single dose of talacotuzumab 9 milligram per kilogram (mg/kg) intravenously (IV) every two weeks.

Serious adverse events	Daratumumab	Talacotuzumab	
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 33 (45.45%)	1 / 1 (100.00%)	
number of deaths (all causes)	6	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatic Cancer			
subjects affected / exposed	1 / 33 (3.03%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 33 (3.03%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib Fracture			

subjects affected / exposed	1 / 33 (3.03%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hand Fracture			
subjects affected / exposed	1 / 33 (3.03%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Thrombophlebitis Superficial			
subjects affected / exposed	1 / 33 (3.03%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial Fibrillation			
subjects affected / exposed	1 / 33 (3.03%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute Coronary Syndrome			
subjects affected / exposed	1 / 33 (3.03%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Failure			
subjects affected / exposed	1 / 33 (3.03%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Failure Congestive			
subjects affected / exposed	1 / 33 (3.03%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Transient Ischaemic Attack			
subjects affected / exposed	1 / 33 (3.03%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 33 (3.03%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	3 / 33 (9.09%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Autoimmune Disorder			
subjects affected / exposed	1 / 33 (3.03%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 33 (3.03%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal Haemorrhage			
subjects affected / exposed	1 / 33 (3.03%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic Obstructive Pulmonary Disease			
subjects affected / exposed	1 / 33 (3.03%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 33 (0.00%)	1 / 1 (100.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal Oedema			

subjects affected / exposed	1 / 33 (3.03%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Corona Virus Infection			
subjects affected / exposed	1 / 33 (3.03%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung Infection			
subjects affected / exposed	1 / 33 (3.03%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 33 (3.03%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung Infection Pseudomonal			
subjects affected / exposed	1 / 33 (3.03%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory Tract Infection			
subjects affected / exposed	1 / 33 (3.03%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	3 / 33 (9.09%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypernatraemia			
subjects affected / exposed	1 / 33 (3.03%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic Acidosis			

subjects affected / exposed	0 / 33 (0.00%)	1 / 1 (100.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Daratumumab	Talacotuzumab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	33 / 33 (100.00%)	1 / 1 (100.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	5 / 33 (15.15%)	0 / 1 (0.00%)	
occurrences (all)	5	0	
Hypotension			
subjects affected / exposed	2 / 33 (6.06%)	0 / 1 (0.00%)	
occurrences (all)	3	0	
Pallor			
subjects affected / exposed	2 / 33 (6.06%)	0 / 1 (0.00%)	
occurrences (all)	2	0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	6 / 33 (18.18%)	0 / 1 (0.00%)	
occurrences (all)	6	0	
Chills			
subjects affected / exposed	2 / 33 (6.06%)	0 / 1 (0.00%)	
occurrences (all)	2	0	
Asthenia			
subjects affected / exposed	6 / 33 (18.18%)	0 / 1 (0.00%)	
occurrences (all)	8	0	
Pyrexia			
subjects affected / exposed	8 / 33 (24.24%)	0 / 1 (0.00%)	
occurrences (all)	13	0	
Peripheral Swelling			
subjects affected / exposed	2 / 33 (6.06%)	0 / 1 (0.00%)	
occurrences (all)	2	0	
Oedema Peripheral			

subjects affected / exposed	6 / 33 (18.18%)	0 / 1 (0.00%)	
occurrences (all)	6	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	6 / 33 (18.18%)	0 / 1 (0.00%)	
occurrences (all)	8	0	
Dyspnoea			
subjects affected / exposed	4 / 33 (12.12%)	0 / 1 (0.00%)	
occurrences (all)	5	0	
Dyspnoea Exertional			
subjects affected / exposed	2 / 33 (6.06%)	0 / 1 (0.00%)	
occurrences (all)	2	0	
Investigations			
Weight Decreased			
subjects affected / exposed	2 / 33 (6.06%)	0 / 1 (0.00%)	
occurrences (all)	3	0	
Blood Creatinine Increased			
subjects affected / exposed	2 / 33 (6.06%)	0 / 1 (0.00%)	
occurrences (all)	2	0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	3 / 33 (9.09%)	0 / 1 (0.00%)	
occurrences (all)	3	0	
Infusion Related Reaction			
subjects affected / exposed	4 / 33 (12.12%)	0 / 1 (0.00%)	
occurrences (all)	4	0	
Cardiac disorders			
Atrial Fibrillation			
subjects affected / exposed	3 / 33 (9.09%)	0 / 1 (0.00%)	
occurrences (all)	4	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 33 (6.06%)	0 / 1 (0.00%)	
occurrences (all)	2	0	
Headache			

subjects affected / exposed	5 / 33 (15.15%)	0 / 1 (0.00%)	
occurrences (all)	7	0	
Paraesthesia			
subjects affected / exposed	2 / 33 (6.06%)	0 / 1 (0.00%)	
occurrences (all)	4	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	6 / 33 (18.18%)	0 / 1 (0.00%)	
occurrences (all)	25	0	
Neutropenia			
subjects affected / exposed	6 / 33 (18.18%)	0 / 1 (0.00%)	
occurrences (all)	32	0	
Thrombocytopenia			
subjects affected / exposed	9 / 33 (27.27%)	0 / 1 (0.00%)	
occurrences (all)	18	0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	2 / 33 (6.06%)	0 / 1 (0.00%)	
occurrences (all)	2	0	
Eye disorders			
Conjunctival Haemorrhage			
subjects affected / exposed	2 / 33 (6.06%)	0 / 1 (0.00%)	
occurrences (all)	2	0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	7 / 33 (21.21%)	0 / 1 (0.00%)	
occurrences (all)	9	0	
Constipation			
subjects affected / exposed	5 / 33 (15.15%)	0 / 1 (0.00%)	
occurrences (all)	5	0	
Nausea			
subjects affected / exposed	3 / 33 (9.09%)	1 / 1 (100.00%)	
occurrences (all)	3	1	
Vomiting			
subjects affected / exposed	3 / 33 (9.09%)	1 / 1 (100.00%)	
occurrences (all)	4	1	
Hepatobiliary disorders			

Hyperbilirubinaemia			
subjects affected / exposed	2 / 33 (6.06%)	0 / 1 (0.00%)	
occurrences (all)	10	0	
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	3 / 33 (9.09%)	0 / 1 (0.00%)	
occurrences (all)	3	0	
Night Sweats			
subjects affected / exposed	2 / 33 (6.06%)	0 / 1 (0.00%)	
occurrences (all)	2	0	
Pruritus			
subjects affected / exposed	2 / 33 (6.06%)	0 / 1 (0.00%)	
occurrences (all)	2	0	
Renal and urinary disorders			
Renal Impairment			
subjects affected / exposed	0 / 33 (0.00%)	1 / 1 (100.00%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	3 / 33 (9.09%)	0 / 1 (0.00%)	
occurrences (all)	3	0	
Arthralgia			
subjects affected / exposed	2 / 33 (6.06%)	0 / 1 (0.00%)	
occurrences (all)	3	0	
Muscle Spasms			
subjects affected / exposed	2 / 33 (6.06%)	0 / 1 (0.00%)	
occurrences (all)	2	0	
Musculoskeletal Chest Pain			
subjects affected / exposed	2 / 33 (6.06%)	0 / 1 (0.00%)	
occurrences (all)	2	0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	3 / 33 (9.09%)	0 / 1 (0.00%)	
occurrences (all)	4	0	
Urinary Tract Infection			

subjects affected / exposed	4 / 33 (12.12%)	0 / 1 (0.00%)	
occurrences (all)	4	0	
Pneumonia			
subjects affected / exposed	2 / 33 (6.06%)	0 / 1 (0.00%)	
occurrences (all)	2	0	
Herpes Simplex			
subjects affected / exposed	2 / 33 (6.06%)	0 / 1 (0.00%)	
occurrences (all)	2	0	
Campylobacter Infection			
subjects affected / exposed	2 / 33 (6.06%)	0 / 1 (0.00%)	
occurrences (all)	2	0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	3 / 33 (9.09%)	0 / 1 (0.00%)	
occurrences (all)	3	0	
Type 2 Diabetes Mellitus			
subjects affected / exposed	2 / 33 (6.06%)	0 / 1 (0.00%)	
occurrences (all)	2	0	
Hyperglycaemia			
subjects affected / exposed	3 / 33 (9.09%)	0 / 1 (0.00%)	
occurrences (all)	7	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 March 2017	The purpose of this amendment was: clarification was provided for subject monitoring and availability of resuscitation equipment in the event of a fatal infusion related reaction (IRR) event during talacotuzumab infusion in study 56022473AML2002. Infusion-rate guidance was changed, and duration of monitoring was increased from 30 minutes to 1-hour post-infusion. Dosing schedules were clarified for talacotuzumab and daratumumab, pre-infusion medications were added for talacotuzumab, pre- and post-infusion medications were added/or clarified for daratumumab. Requirement for blood type assessment and indirect antiglobulin results on Cycle 1 Day 1 for daratumumab and recommendation for herpes zoster (HZ) reactivation prophylaxis were added. Storage and central laboratory information were also included.
25 April 2017	The purpose of this amendment was: closed the enrollment to the talacotuzumab arm as a precautionary measure due to the benefit/risk considerations in subjects with low-risk myelodysplastic syndromes (MDS) and based on the occurrence of a serious Grade 4 IRR in the first subject who received the first and only dose of talacotuzumab in this study.

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.

Analyses in this study are limited to data from daratumumab arm only. Objectives initially designed to explore efficacy, PK and safety in talacotuzumab arm were not pursued as enrollment was stopped due to occurrence of serious Grade 4 IRR.

Notes: