

**Clinical trial results:****A Randomized, Double-Blind, Phase 3 Study to Evaluate the Activity of Momelotinib (MMB) versus Danazol (DAN) in Symptomatic, Anemic Subjects with Primary Myelofibrosis (PMF), Post-Polycythemia Vera (PV) Myelofibrosis, or Post Essential Thrombocythemia (ET) Myelofibrosis who were Previously Treated with JAK Inhibitor Therapy****Summary**

EudraCT number	2019-000583-18
Trial protocol	GB DE SE DK FR CZ ES PL HU AT IT RO
Global end of trial date	29 December 2022

Results information

Result version number	v1
This version publication date	11 August 2023
First version publication date	11 August 2023

Trial information**Trial identification**

Sponsor protocol code	SRA-MMB-301
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04173494
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Sierra Oncology LLC – a GSK company
Sponsor organisation address	980 Great West Road, Brentford, Middlesex, United Kingdom, TW8 9GS
Public contact	GSK Response Center, Sierra Oncology, a GlaxoSmithKline company, 1 877-379-3718, GSKClinicalSupportHD@gsk.com
Scientific contact	GSK Response Center, Sierra Oncology LLC – a GSK company, 1 877-379-3718, GSKClinicalSupportHD@gsk.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	14 April 2023
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	29 December 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the efficacy of MMB versus DAN assessed by improvement in Myelofibrosis Symptom Assessment Form version (v) 4.0 (MFSAF) total symptom score (TSS) in participants with PMF, post-PV myelofibrosis (MF), or post-ET MF who were previously treated with approved Janus kinase (JAK) inhibitor therapy

Protection of trial subjects:

Not applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 February 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 5
Country: Number of subjects enrolled	Austria: 2
Country: Number of subjects enrolled	Belgium: 6
Country: Number of subjects enrolled	Bulgaria: 5
Country: Number of subjects enrolled	Canada: 5
Country: Number of subjects enrolled	Czechia: 1
Country: Number of subjects enrolled	Denmark: 2
Country: Number of subjects enrolled	France: 13
Country: Number of subjects enrolled	Germany: 14
Country: Number of subjects enrolled	Hungary: 13
Country: Number of subjects enrolled	Israel: 18
Country: Number of subjects enrolled	Italy: 32
Country: Number of subjects enrolled	New Zealand: 2
Country: Number of subjects enrolled	Poland: 14
Country: Number of subjects enrolled	Romania: 8
Country: Number of subjects enrolled	Singapore: 4
Country: Number of subjects enrolled	Korea, Republic of: 11
Country: Number of subjects enrolled	Spain: 9
Country: Number of subjects enrolled	Taiwan: 2
Country: Number of subjects enrolled	United Kingdom: 5

Country: Number of subjects enrolled	United States: 24
Worldwide total number of subjects	195
EEA total number of subjects	119

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)	40
From 65 to 84 years	151
85 years and over	4

Subject disposition

Recruitment

Recruitment details:

This study evaluated the activity of Momelotinib (MMB) versus Danazol (DAN) in Symptomatic, Anemic participants. This study consists of Randomized Double-blind (DB) Treatment Period (TP) and Open-label extended Treatment Period (OLP).

Pre-assignment

Screening details:

A total of 195 participants were enrolled in the study.

Period 1

Period 1 title	Randomized DB TP (Up to Week 24)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	MMB 200 mg Once Daily (QD) + Placebo

Arm description:

Participants were randomized to receive 200 milligrams (mg) of MMB orally QD and a DAN-placebo orally twice daily (BID) during the randomized 24-week double-blind treatment period. Participants who completed the randomized treatment period or discontinued treatment early for other reasons but completed scheduled assessments through Week 24 were enrolled in an open-label extended treatment period. Participants continued to receive 200 mg of MMB orally QD during the open-label extended treatment period. Participants who discontinued treatment prior to Week 24 due to splenic progression or other reasons, but completed assessments, were unblinded. Participants who discontinued MMB during the randomized treatment period were not eligible to receive MMB in the open-label extended treatment period. Participants who were randomized to MMB during the randomized treatment period with confirmed splenic progression could not proceed to the open-label extended treatment period.

Arm type	Experimental
Investigational medicinal product name	Placebo matching DAN
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Placebo matching DAN was administered orally BID

Investigational medicinal product name	MMB 200 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

MMB was administered with a dose of 200 mg orally QD.

Arm title	DAN 300 mg BID + Placebo
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Arm description:

Participants were randomized to receive 300 mg of DAN orally BID and MMB-placebo orally QD during the randomized 24-week double-blind treatment period. Participants who completed the randomized treatment period, discontinued treatment early due to splenic progression, or discontinued treatment early for other reasons but completed scheduled assessments through Week 24 enrolled in an open-label extended treatment period. Participants switched to receive 200 mg of MMB orally QD during open-label extended treatment period. All participants elected to receive MMB as open-label treatment during

the open-label extended treatment period.

Arm type	Active comparator
Investigational medicinal product name	Placebo matching MMB
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo matching MMB was administered orally QD

Investigational medicinal product name	DAN 300 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

DAN was administered with a dose of 300 mg orally BID.

Number of subjects in period 1	MMB 200 mg Once Daily (QD) + Placebo	DAN 300 mg BID + Placebo
Started	130	65
Completed	94	38
Not completed	36	27
Adverse event, serious fatal	9	7
Consent withdrawn by subject	6	5
Physician decision	-	1
Leukemic Transformation	2	2
Adverse event, non-fatal	7	4
Death	4	3
Lost to follow-up	1	-
Disease Progression	1	2
Lack of efficacy	6	3

Period 2

Period 2 title	Open-Label extended TP(Weeks 24 to 77.6)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
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Arm title	MMB 200 mg Once Daily (QD) + Placebo
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Arm description:

Participants were randomized to receive 200 milligrams (mg) of MMB orally QD and a DAN-placebo orally twice daily (BID) during the randomized 24-week double-blind treatment period. Participants who completed the randomized treatment period or discontinued treatment early for other reasons but completed scheduled assessments through Week 24 were enrolled in an open-label extended treatment period. Participants continued to receive 200 mg of MMB orally QD during the open-label extended treatment period.

Participants who discontinued treatment prior to Week 24 due to splenic progression or other reasons, but completed assessments, were unblinded. Participants who discontinued MMB during the randomized treatment period were not eligible to receive MMB in the open-label extended treatment period.

Participants who were randomized to MMB during the randomized treatment period with confirmed splenic progression could not proceed to the open-label extended treatment period.

Arm type	Experimental
Investigational medicinal product name	Placebo matching DAN
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Placebo matching DAN was administered orally BID

Investigational medicinal product name	MMB 200 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

MMB was administered with a dose of 200 mg orally QD.

Arm title	DAN 300 mg BID + Placebo
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Arm description:

Participants were randomized to receive 300 mg of DAN orally BID and MMB-placebo orally QD during the randomized 24-week double-blind treatment period. Participants who completed the randomized treatment period, discontinued treatment early due to splenic progression, or discontinued treatment early for other reasons but completed scheduled assessments through Week 24 enrolled in an open-label extended treatment period. Participants switched to receive 200 mg of MMB orally QD during open-label extended treatment period. All participants elected to receive MMB as open-label treatment during the open-label extended treatment period.

Arm type	Active comparator
Investigational medicinal product name	DAN 300 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

DAN was administered with a dose of 300 mg orally BID.

Investigational medicinal product name	Placebo matching MMB
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo matching MMB was administered orally QD

Investigational medicinal product name	MMB 200 mg
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

MMB was administered with a dose of 200 mg orally QD.

Number of subjects in period 2^[1]	MMB 200 mg Once Daily (QD) + Placebo	DAN 300 mg BID + Placebo
Started	93	36
Completed	0	0
Not completed	93	41
Adverse event, serious fatal	8	-
Physician decision	4	3
Consent withdrawn by subject	4	3
Leukemic Transformation	-	1
Adverse event, non-fatal	3	1
Death	6	3
Continuing in MMB extension study	61	27
Disease Progression	1	1
Lack of efficacy	6	2
Joined	0	5
Protocol defined criteria	-	5

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: 93 participants from Randomized Treatment Phase entered in Open-label Phase.

Baseline characteristics

Reporting groups

Reporting group title	MMB 200 mg Once Daily (QD) + Placebo
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Reporting group description:

Participants were randomized to receive 200 milligrams (mg) of MMB orally QD and a DAN-placebo orally twice daily (BID) during the randomized 24-week double-blind treatment period. Participants who completed the randomized treatment period or discontinued treatment early for other reasons but completed scheduled assessments through Week 24 were enrolled in an open-label extended treatment period. Participants continued to receive 200 mg of MMB orally QD during the open-label extended treatment period. Participants who discontinued treatment prior to Week 24 due to splenic progression or other reasons, but completed assessments, were unblinded. Participants who discontinued MMB during the randomized treatment period were not eligible to receive MMB in the open-label extended treatment period. Participants who were randomized to MMB during the randomized treatment period with confirmed splenic progression could not proceed to the open-label extended treatment period.

Reporting group title	DAN 300 mg BID + Placebo
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Reporting group description:

Participants were randomized to receive 300 mg of DAN orally BID and MMB-placebo orally QD during the randomized 24-week double-blind treatment period. Participants who completed the randomized treatment period, discontinued treatment early due to splenic progression, or discontinued treatment early for other reasons but completed scheduled assessments through Week 24 enrolled in an open-label extended treatment period. Participants switched to receive 200 mg of MMB orally QD during open-label extended treatment period. All participants elected to receive MMB as open-label treatment during the open-label extended treatment period.

Reporting group values	MMB 200 mg Once Daily (QD) + Placebo	DAN 300 mg BID + Placebo	Total
Number of subjects	130	65	195
Age categorical			
Baseline characteristics were measured in the Intention-To-Treat (ITT) Analysis Set, which included all randomized participants.			
Units: Participants			
All participants	130	65	195
Age Continuous			
Baseline characteristics were measured in the Intention-To-Treat (ITT) Analysis Set, which included all randomized participants.			
Units: years			
arithmetic mean	69.85	71.46	
standard deviation	± 8.24	± 6.99	-
Sex: Female, Male			
Baseline characteristics were measured in the Intention-To-Treat (ITT) Analysis Set, which included all randomized participants.			
Units: Participants			
Female	51	21	72
Male	79	44	123
Ethnicity (NIH/OMB)			
Baseline characteristics were measured in the Intention-To-Treat (ITT) Analysis Set, which included all randomized participants.			
Units: Subjects			
Hispanic or Latino	5	6	11
Not Hispanic or Latino	115	54	169
Unknown or Not Reported	10	5	15
Race (NIH/OMB)			
Baseline characteristics were measured in the Intention-To-Treat (ITT) Analysis Set, which included all randomized participants.			

randomized participants.			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	12	6	18
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	2	2	4
White	107	50	157
More than one race	0	0	0
Unknown or Not Reported	9	7	16

Subject analysis sets

Subject analysis set title	MMB 200 mg QD + Placebo
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants were randomized to receive 200 milligrams (mg) of MMB orally QD and a DAN-placebo orally twice daily (BID) during the randomized 24-week double-blind treatment period. Participants who completed the randomized treatment period or discontinued treatment early for other reasons but completed scheduled assessments through Week 24 were enrolled in an open-label extended treatment period. Participants continued to receive 200 mg of MMB orally QD during the open-label extended treatment period.

Participants who discontinued treatment prior to Week 24 due to splenic progression or other reasons, but completed assessments, were unblinded. Participants who discontinued MMB during the randomized treatment period were not eligible to receive MMB in the open-label extended treatment period.

Participants who were randomized to MMB during the randomized treatment period with confirmed splenic progression could not proceed to the open-label extended treatment period.

Subject analysis set title	MMB 200 mg QD + Placebo
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants were randomized to receive 200 milligrams (mg) of MMB orally QD and a DAN-placebo orally twice daily (BID) during the randomized 24-week double-blind treatment period. Participants who completed the randomized treatment period or discontinued treatment early for other reasons but completed scheduled assessments through Week 24 were enrolled in an open-label extended treatment period. Participants continued to receive 200 mg of MMB orally QD during the open-label extended treatment period.

Participants who discontinued treatment prior to Week 24 due to splenic progression or other reasons, but completed assessments, were unblinded. Participants who discontinued MMB during the randomized treatment period were not eligible to receive MMB in the open-label extended treatment period.

Participants who were randomized to MMB during the randomized treatment period with confirmed splenic progression could not proceed to the open-label extended treatment period.

Subject analysis set title	MMB 200 mg QD + Placebo
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants were randomized to receive 200 milligrams (mg) of MMB orally QD and a DAN-placebo orally twice daily (BID) during the randomized 24-week double-blind treatment period. Participants who completed the randomized treatment period or discontinued treatment early for other reasons but completed scheduled assessments through Week 24 were enrolled in an open-label extended treatment period. Participants continued to receive 200 mg of MMB orally QD during the open-label extended treatment period.

Participants who discontinued treatment prior to Week 24 due to splenic progression or other reasons, but completed assessments, were unblinded. Participants who discontinued MMB during the randomized treatment period were not eligible to receive MMB in the open-label extended treatment period.

Participants who were randomized to MMB during the randomized treatment period with confirmed splenic progression could not proceed to the open-label extended treatment period.

Subject analysis set title	MMB 200 mg QD + Placebo
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants were randomized to receive 200 milligrams (mg) of MMB orally QD and a DAN-placebo orally twice daily (BID) during the randomized 24-week double-blind treatment period. Participants who completed the randomized treatment period or discontinued treatment early for other reasons but

completed scheduled assessments through Week 24 were enrolled in an open-label extended treatment period. Participants continued to receive 200 mg of MMB orally QD during the open-label extended treatment period.

Participants who discontinued treatment prior to Week 24 due to splenic progression or other reasons, but completed assessments, were unblinded. Participants who discontinued MMB during the randomized treatment period were not eligible to receive MMB in the open-label extended treatment period.

Participants who were randomized to MMB during the randomized treatment period with confirmed splenic progression could not proceed to the open-label extended treatment period.

Subject analysis set title	MMB 200 mg QD + Placebo
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants were randomized to receive 200 milligrams (mg) of MMB orally QD and a DAN-placebo orally twice daily (BID) during the randomized 24-week double-blind treatment period. Participants who completed the randomized treatment period or discontinued treatment early for other reasons but completed scheduled assessments through Week 24 were enrolled in an open-label extended treatment period. Participants continued to receive 200 mg of MMB orally QD during the open-label extended treatment period.

Participants who discontinued treatment prior to Week 24 due to splenic progression or other reasons, but completed assessments, were unblinded. Participants who discontinued MMB during the randomized treatment period were not eligible to receive MMB in the open-label extended treatment period.

Participants who were randomized to MMB during the randomized treatment period with confirmed splenic progression could not proceed to the open-label extended treatment period.

Subject analysis set title	MMB 200 mg QD + Placebo- Randomized DB TP
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants were randomized to receive 200 mg of MMB orally QD and a DAN-placebo orally BID during the randomized 24-week double-blind treatment period.

Subject analysis set title	DAN 300 mg BID + Placebo- Randomized DB TP
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants were randomized to receive 300 mg of DAN orally BID and MMB-placebo orally QD during the randomized 24-week double-blind treatment period.

Subject analysis set title	MMB 200 mg QD- Open-Label Extended TP
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants who completed the randomized treatment period or discontinued treatment early for other reasons but completed scheduled assessments through Week 24 were enrolled in an open-label extended treatment period. Participants continued to receive 200 mg of MMB orally QD during the open-label extended treatment period.

Subject analysis set title	DAN 300 mg BID to MMB 200 mg QD- Open-Label Extended TP
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants who completed the randomized treatment period, discontinued treatment early due to splenic progression, or discontinued treatment early for other reasons but completed scheduled assessments through Week 24 were enrolled in an open-label extended treatment period. Participants who received DAN 300 mg BID during randomized period switched to receive 200 mg of MMB orally QD during open-label extended treatment period.

Subject analysis set title	MMB 200 mg QD + Placebo
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants were randomized to receive 200 milligrams (mg) of MMB orally QD and a DAN-placebo orally twice daily (BID) during the randomized 24-week double-blind treatment period. Participants who completed the randomized treatment period or discontinued treatment early for other reasons but completed scheduled assessments through Week 24 were enrolled in an open-label extended treatment period. Participants continued to receive 200 mg of MMB orally QD during the open-label extended treatment period.

Participants who discontinued treatment prior to Week 24 due to splenic progression or other reasons, but completed assessments, were unblinded. Participants who discontinued MMB during the randomized treatment period were not eligible to receive MMB in the open-label extended treatment period.

Participants who were randomized to MMB during the randomized treatment period with confirmed splenic progression could not proceed to the open-label extended treatment period.

Reporting group values	MMB 200 mg QD + Placebo	MMB 200 mg QD + Placebo	MMB 200 mg QD + Placebo
Number of subjects	130	92	32
Age categorical			
Baseline characteristics were measured in the Intention-To-Treat (ITT) Analysis Set, which included all randomized participants.			
Units: Participants			
All participants			
Age Continuous			
Baseline characteristics were measured in the Intention-To-Treat (ITT) Analysis Set, which included all randomized participants.			
Units: years			
arithmetic mean			
standard deviation	±	±	±
Sex: Female, Male			
Baseline characteristics were measured in the Intention-To-Treat (ITT) Analysis Set, which included all randomized participants.			
Units: Participants			
Female			
Male			
Ethnicity (NIH/OMB)			
Baseline characteristics were measured in the Intention-To-Treat (ITT) Analysis Set, which included all randomized participants.			
Units: Subjects			
Hispanic or Latino			
Not Hispanic or Latino			
Unknown or Not Reported			
Race (NIH/OMB)			
Baseline characteristics were measured in the Intention-To-Treat (ITT) Analysis Set, which included all randomized participants.			
Units: Subjects			
American Indian or Alaska Native	0		
Asian	12		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	2		
White	107		
More than one race	0		
Unknown or Not Reported	9		

Reporting group values	MMB 200 mg QD + Placebo	MMB 200 mg QD + Placebo	MMB 200 mg QD + Placebo- Randomized DB TP
Number of subjects	40	63	130
Age categorical			
Baseline characteristics were measured in the Intention-To-Treat (ITT) Analysis Set, which included all randomized participants.			
Units: Participants			
All participants			
Age Continuous			
Baseline characteristics were measured in the Intention-To-Treat (ITT) Analysis Set, which included all randomized participants.			
Units: years			
arithmetic mean			
standard deviation	±	±	±

Sex: Female, Male			
Baseline characteristics were measured in the Intention-To-Treat (ITT) Analysis Set, which included all randomized participants.			
Units: Participants			
Female			
Male			
Ethnicity (NIH/OMB)			
Baseline characteristics were measured in the Intention-To-Treat (ITT) Analysis Set, which included all randomized participants.			
Units: Subjects			
Hispanic or Latino			
Not Hispanic or Latino			
Unknown or Not Reported			
Race (NIH/OMB)			
Baseline characteristics were measured in the Intention-To-Treat (ITT) Analysis Set, which included all randomized participants.			
Units: Subjects			
American Indian or Alaska Native			
Asian			
Native Hawaiian or Other Pacific Islander			
Black or African American			
White			
More than one race			
Unknown or Not Reported			

Reporting group values	DAN 300 mg BID + Placebo-Randomized DB TP	MMB 200 mg QD-Open-Label Extended TP	DAN 300 mg BID to MMB 200 mg QD-Open-Label Extended TP
Number of subjects	65	93	41
Age categorical			
Baseline characteristics were measured in the Intention-To-Treat (ITT) Analysis Set, which included all randomized participants.			
Units: Participants			
All participants			
Age Continuous			
Baseline characteristics were measured in the Intention-To-Treat (ITT) Analysis Set, which included all randomized participants.			
Units: years			
arithmetic mean			
standard deviation	±	±	±
Sex: Female, Male			
Baseline characteristics were measured in the Intention-To-Treat (ITT) Analysis Set, which included all randomized participants.			
Units: Participants			
Female			
Male			
Ethnicity (NIH/OMB)			
Baseline characteristics were measured in the Intention-To-Treat (ITT) Analysis Set, which included all randomized participants.			
Units: Subjects			
Hispanic or Latino			
Not Hispanic or Latino			
Unknown or Not Reported			

Race (NIH/OMB)			
Baseline characteristics were measured in the Intention-To-Treat (ITT) Analysis Set, which included all randomized participants.			
Units: Subjects			
American Indian or Alaska Native Asian Native Hawaiian or Other Pacific Islander Black or African American White More than one race Unknown or Not Reported			

Reporting group values	MMB 200 mg QD + Placebo		
Number of subjects	89		
Age categorical			
Baseline characteristics were measured in the Intention-To-Treat (ITT) Analysis Set, which included all randomized participants.			
Units: Participants			
All participants			
Age Continuous			
Baseline characteristics were measured in the Intention-To-Treat (ITT) Analysis Set, which included all randomized participants.			
Units: years			
arithmetic mean			
standard deviation	±		
Sex: Female, Male			
Baseline characteristics were measured in the Intention-To-Treat (ITT) Analysis Set, which included all randomized participants.			
Units: Participants			
Female			
Male			
Ethnicity (NIH/OMB)			
Baseline characteristics were measured in the Intention-To-Treat (ITT) Analysis Set, which included all randomized participants.			
Units: Subjects			
Hispanic or Latino			
Not Hispanic or Latino			
Unknown or Not Reported			
Race (NIH/OMB)			
Baseline characteristics were measured in the Intention-To-Treat (ITT) Analysis Set, which included all randomized participants.			
Units: Subjects			
American Indian or Alaska Native Asian Native Hawaiian or Other Pacific Islander Black or African American White More than one race Unknown or Not Reported			

End points

End points reporting groups

Reporting group title	MMB 200 mg Once Daily (QD) + Placebo
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Reporting group description:

Participants were randomized to receive 200 milligrams (mg) of MMB orally QD and a DAN-placebo orally twice daily (BID) during the randomized 24-week double-blind treatment period. Participants who completed the randomized treatment period or discontinued treatment early for other reasons but completed scheduled assessments through Week 24 were enrolled in an open-label extended treatment period. Participants continued to receive 200 mg of MMB orally QD during the open-label extended treatment period. Participants who discontinued treatment prior to Week 24 due to splenic progression or other reasons, but completed assessments, were unblinded. Participants who discontinued MMB during the randomized treatment period were not eligible to receive MMB in the open-label extended treatment period. Participants who were randomized to MMB during the randomized treatment period with confirmed splenic progression could not proceed to the open-label extended treatment period.

Reporting group title	DAN 300 mg BID + Placebo
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Reporting group description:

Participants were randomized to receive 300 mg of DAN orally BID and MMB-placebo orally QD during the randomized 24-week double-blind treatment period. Participants who completed the randomized treatment period, discontinued treatment early due to splenic progression, or discontinued treatment early for other reasons but completed scheduled assessments through Week 24 enrolled in an open-label extended treatment period. Participants switched to receive 200 mg of MMB orally QD during open-label extended treatment period. All participants elected to receive MMB as open-label treatment during the open-label extended treatment period.

Reporting group title	MMB 200 mg Once Daily (QD) + Placebo
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Reporting group description:

Participants were randomized to receive 200 milligrams (mg) of MMB orally QD and a DAN-placebo orally twice daily (BID) during the randomized 24-week double-blind treatment period. Participants who completed the randomized treatment period or discontinued treatment early for other reasons but completed scheduled assessments through Week 24 were enrolled in an open-label extended treatment period. Participants continued to receive 200 mg of MMB orally QD during the open-label extended treatment period.

Participants who discontinued treatment prior to Week 24 due to splenic progression or other reasons, but completed assessments, were unblinded. Participants who discontinued MMB during the randomized treatment period were not eligible to receive MMB in the open-label extended treatment period. Participants who were randomized to MMB during the randomized treatment period with confirmed splenic progression could not proceed to the open-label extended treatment period.

Reporting group title	DAN 300 mg BID + Placebo
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Reporting group description:

Participants were randomized to receive 300 mg of DAN orally BID and MMB-placebo orally QD during the randomized 24-week double-blind treatment period. Participants who completed the randomized treatment period, discontinued treatment early due to splenic progression, or discontinued treatment early for other reasons but completed scheduled assessments through Week 24 enrolled in an open-label extended treatment period. Participants switched to receive 200 mg of MMB orally QD during open-label extended treatment period. All participants elected to receive MMB as open-label treatment during the open-label extended treatment period.

Subject analysis set title	MMB 200 mg QD + Placebo
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

Participants were randomized to receive 200 milligrams (mg) of MMB orally QD and a DAN-placebo orally twice daily (BID) during the randomized 24-week double-blind treatment period. Participants who completed the randomized treatment period or discontinued treatment early for other reasons but completed scheduled assessments through Week 24 were enrolled in an open-label extended treatment period. Participants continued to receive 200 mg of MMB orally QD during the open-label extended treatment period.

Participants who discontinued treatment prior to Week 24 due to splenic progression or other reasons, but completed assessments, were unblinded. Participants who discontinued MMB during the randomized treatment period were not eligible to receive MMB in the open-label extended treatment period. Participants who were randomized to MMB during the randomized treatment period with confirmed splenic progression could not proceed to the open-label extended treatment period.

Subject analysis set title	MMB 200 mg QD + Placebo
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

Participants were randomized to receive 200 milligrams (mg) of MMB orally QD and a DAN-placebo orally twice daily (BID) during the randomized 24-week double-blind treatment period. Participants who completed the randomized treatment period or discontinued treatment early for other reasons but completed scheduled assessments through Week 24 were enrolled in an open-label extended treatment period. Participants continued to receive 200 mg of MMB orally QD during the open-label extended treatment period.

Participants who discontinued treatment prior to Week 24 due to splenic progression or other reasons, but completed assessments, were unblinded. Participants who discontinued MMB during the randomized treatment period were not eligible to receive MMB in the open-label extended treatment period.

Participants who were randomized to MMB during the randomized treatment period with confirmed splenic progression could not proceed to the open-label extended treatment period.

Subject analysis set title	MMB 200 mg QD + Placebo
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants were randomized to receive 200 milligrams (mg) of MMB orally QD and a DAN-placebo orally twice daily (BID) during the randomized 24-week double-blind treatment period. Participants who completed the randomized treatment period or discontinued treatment early for other reasons but completed scheduled assessments through Week 24 were enrolled in an open-label extended treatment period. Participants continued to receive 200 mg of MMB orally QD during the open-label extended treatment period.

Participants who discontinued treatment prior to Week 24 due to splenic progression or other reasons, but completed assessments, were unblinded. Participants who discontinued MMB during the randomized treatment period were not eligible to receive MMB in the open-label extended treatment period.

Participants who were randomized to MMB during the randomized treatment period with confirmed splenic progression could not proceed to the open-label extended treatment period.

Subject analysis set title	MMB 200 mg QD + Placebo
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants were randomized to receive 200 milligrams (mg) of MMB orally QD and a DAN-placebo orally twice daily (BID) during the randomized 24-week double-blind treatment period. Participants who completed the randomized treatment period or discontinued treatment early for other reasons but completed scheduled assessments through Week 24 were enrolled in an open-label extended treatment period. Participants continued to receive 200 mg of MMB orally QD during the open-label extended treatment period.

Participants who discontinued treatment prior to Week 24 due to splenic progression or other reasons, but completed assessments, were unblinded. Participants who discontinued MMB during the randomized treatment period were not eligible to receive MMB in the open-label extended treatment period.

Participants who were randomized to MMB during the randomized treatment period with confirmed splenic progression could not proceed to the open-label extended treatment period.

Subject analysis set title	MMB 200 mg QD + Placebo
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants were randomized to receive 200 milligrams (mg) of MMB orally QD and a DAN-placebo orally twice daily (BID) during the randomized 24-week double-blind treatment period. Participants who completed the randomized treatment period or discontinued treatment early for other reasons but completed scheduled assessments through Week 24 were enrolled in an open-label extended treatment period. Participants continued to receive 200 mg of MMB orally QD during the open-label extended treatment period.

Participants who discontinued treatment prior to Week 24 due to splenic progression or other reasons, but completed assessments, were unblinded. Participants who discontinued MMB during the randomized treatment period were not eligible to receive MMB in the open-label extended treatment period.

Participants who were randomized to MMB during the randomized treatment period with confirmed splenic progression could not proceed to the open-label extended treatment period.

Subject analysis set title	MMB 200 mg QD + Placebo- Randomized DB TP
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants were randomized to receive 200 mg of MMB orally QD and a DAN-placebo orally BID during the randomized 24-week double-blind treatment period.

Subject analysis set title	DAN 300 mg BID + Placebo- Randomized DB TP
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants were randomized to receive 300 mg of DAN orally BID and MMB-placebo orally QD during

the randomized 24-week double-blind treatment period.

Subject analysis set title	MMB 200 mg QD- Open-Label Extended TP
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants who completed the randomized treatment period or discontinued treatment early for other reasons but completed scheduled assessments through Week 24 were enrolled in an open-label extended treatment period. Participants continued to receive 200 mg of MMB orally QD during the open-label extended treatment period.

Subject analysis set title	DAN 300 mg BID to MMB 200 mg QD- Open-Label Extended TP
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants who completed the randomized treatment period, discontinued treatment early due to splenic progression, or discontinued treatment early for other reasons but completed scheduled assessments through Week 24 were enrolled in an open-label extended treatment period. Participants who received DAN 300 mg BID during randomized period switched to receive 200 mg of MMB orally QD during open-label extended treatment period.

Subject analysis set title	MMB 200 mg QD + Placebo
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants were randomized to receive 200 milligrams (mg) of MMB orally QD and a DAN-placebo orally twice daily (BID) during the randomized 24-week double-blind treatment period. Participants who completed the randomized treatment period or discontinued treatment early for other reasons but completed scheduled assessments through Week 24 were enrolled in an open-label extended treatment period. Participants continued to receive 200 mg of MMB orally QD during the open-label extended treatment period.

Participants who discontinued treatment prior to Week 24 due to splenic progression or other reasons, but completed assessments, were unblinded. Participants who discontinued MMB during the randomized treatment period were not eligible to receive MMB in the open-label extended treatment period.

Participants who were randomized to MMB during the randomized treatment period with confirmed splenic progression could not proceed to the open-label extended treatment period.

Primary: Total Symptom Score (TSS) Response Rate at Week 24

End point title	Total Symptom Score (TSS) Response Rate at Week 24 ^[1]
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End point description:

Myelofibrosis Symptom Assessment Form (MFSAF) TSS version (v) 4.0 response rate was defined as percentage of participants with a ≥ 50 percent (%) reduction from Baseline in mean MFSAF TSS over consecutive 28-day period immediately before end of Week 24. TSS response rate was measured using MFSAF v4.0. MFSAF v4.0 comprises 7 domains representing 7 most relevant symptoms of myelofibrosis (MF) identified through existing participant and clinician-based evidence: fatigue,night sweats,pruritus,abdominal discomfort,pain under left ribs,early satietyand bone pain. Participants scored each symptom domain using an 11-point numeric rating scale ranging from 0(absent) to 10(worst imaginable). The MFSAF TSS was calculated as sum of scores of 7 domains for a possible range of scores of 0 to 70, with a higher TSS corresponding to more severe symptoms. A reduction from Baseline corresponded to a lessening of MF symptoms. Baseline was the last assessment done before or on the day of first dose date

End point type	Primary
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End point timeframe:

Baseline and Week 24

Notes:

[1] - 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 is only reporting on a subset of the arms that are contained in the Baseline period.

End point values	DAN 300 mg BID + Placebo	MMB 200 mg QD + Placebo		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	65 ^[2]	130 ^[3]		
Units: Percentage of participants				
number (confidence interval 95%)	9.23 (3.46 to 19.02)	24.62 (17.49 to 32.94)		

Notes:

[2] - Intent-To-Treat (ITT) Analysis Set, which included all randomized participants

[3] - Intent-To-Treat (ITT) Analysis Set, which included all randomized participants

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	DAN 300 mg BID + Placebo v MMB 200 mg QD + Placebo
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0095
Method	Cochran-Mantel-Haenszel
Parameter estimate	Stratified Cochran-Mantel-Haenszel
Point estimate	15.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.54
upper limit	25.81

Primary: Percentage of Participants with Transfusion Independence (TI) at Week 24

End point title	Percentage of Participants with Transfusion Independence (TI) at Week 24 ^[4]
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End point description:

TI status was defined as not receiving red blood cell (RBC) or whole blood transfusion for ≥ 12 weeks, with no hemoglobin (Hgb) level < 8 grams per deciliter (g/dL) during the same interval. Percentage of participants with TI have been presented.

End point type	Primary
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End point timeframe:

Week 24

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 is only reporting on a subset of the arms that are contained in the Baseline period.

End point values	DAN 300 mg BID + Placebo	MMB 200 mg QD + Placebo		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	65 ^[5]	130 ^[6]		
Units: Percentage of Participants				
number (confidence interval 95%)	20.00 (11.10 to 31.77)	30.0 (22.28 to 38.66)		

Notes:

[5] - ITT Analysis Set

[6] - ITT Analysis Set

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: If the lower bound of the confidence interval (CI) is greater than 0, MMB was to be declared non-inferior to DAN.	
Comparison groups	DAN 300 mg BID + Placebo v MMB 200 mg QD + Placebo
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[7]
P-value	= 0.0116
Method	Cochran-Mantel-Haenszel
Parameter estimate	Non-inferiority difference
Point estimate	13.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.86
upper limit	25.3

Notes:

[7] - Non-inferiority difference, defined as $p(\text{MMB}) - (0.8) * p(\text{DAN})$ where $p(\text{MMB})$ is percentage of participants with TI status in MMB arm and $p(\text{DAN})$ is percentage of participants with TI status in DAN arm.

Secondary: Splenic Response Rate (SRR) of $\geq 25\%$ at Week 24

End point title	Splenic Response Rate (SRR) of $\geq 25\%$ at Week 24 ^[8]
End point description: Splenic response rate (SRR) is defined as the percentage of participants who have reduction in spleen volume of $\geq 25\%$ from Baseline at the end of Week 24. Baseline was the last assessment done before or on the day of first dose date.	
End point type	Secondary
End point timeframe: Baseline and Week 24	

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 is only reporting on a subset of the arms that are contained in the Baseline period.

End point values	DAN 300 mg BID + Placebo	MMB 200 mg QD + Placebo		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	65 ^[9]	130 ^[10]		
Units: Percentage of Participants				
number (confidence interval 95%)	6.15 (1.70 to 15.01)	39.23 (30.79 to 48.18)		

Notes:

[9] - ITT Analysis Set

[10] - ITT Analysis Set

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	DAN 300 mg BID + Placebo v MMB 200 mg QD + Placebo
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Stratified Cochran-Mantel-Haenszel
Point estimate	33.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	22.59
upper limit	43.51

Secondary: Change from Baseline in MFSAF TSS at Week 24

End point title	Change from Baseline in MFSAF TSS at Week 24 ^[11]
End point description:	<p>TSS was measured using the MFSAF v4.0. The MFSAF v4.0 comprises 7 domains representing the 7 most relevant symptoms of MF identified through existing participant and clinician-based evidence: fatigue, night sweats, pruritus, abdominal discomfort, pain under the left ribs, early satiety, and bone pain. Participants scored each symptom domain using an 11-point numeric rating scale ranging from 0 (absent) to 10 (worst imaginable). The MFSAF TSS was calculated as the sum of scores of the 7 domains for a possible range of scores of 0 to 70, with a higher TSS corresponding to more severe symptoms. A reduction from Baseline corresponded to a lessening of MF symptoms. Baseline was the last assessment done before or on the day of first dose date. Change from Baseline was defined as the post-Baseline value minus Baseline value. Only those participants with data available at specified time points were analyzed.</p>
End point type	Secondary
End point timeframe:	Baseline and Week 24

Notes:

[11] - 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 is only reporting on a subset of the arms that are contained in the Baseline period.

End point values	DAN 300 mg BID + Placebo	MMB 200 mg QD + Placebo		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	37 ^[12]	92 ^[13]		
Units: Scores on a scale				
least squares mean (standard error)	-3.13 (± 1.62)	-9.36 (± 1.08)		

Notes:

[12] - ITT Analysis Set

[13] - ITT Analysis Set

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	DAN 300 mg BID + Placebo v MMB 200 mg QD + Placebo
Number of subjects included in analysis	129
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0014
Method	mixed model for repeated measures (MMRM)
Parameter estimate	Least Squares Mean Difference
Point estimate	-6.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10
upper limit	-2.43

Secondary: Splenic Response Rate (SRR) of >= 35% at Week 24

End point title	Splenic Response Rate (SRR) of >= 35% at Week 24 ^[14]
End point description:	Splenic response rate (SRR) is defined as the percentage of participants who have reduction in spleen volume of >=35 % from Baseline at the end of Week 24. Baseline was the last assessment done before or on the day of first dose date.
End point type	Secondary
End point timeframe:	Baseline and Week 24

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 is only reporting on a subset of the arms that are contained in the Baseline period.

End point values	DAN 300 mg BID + Placebo	MMB 200 mg QD + Placebo		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	65 ^[15]	130 ^[16]		
Units: Percentage of Participants				
number (confidence interval 95%)	3.08 (0.37 to 10.68)	22.31 (15.48 to 30.44)		

Notes:

[15] - ITT Analysis Set

[16] - ITT Analysis Set

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	DAN 300 mg BID + Placebo v MMB 200 mg QD + Placebo
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0011
Method	Cochran-Mantel-Haenszel
Parameter estimate	Stratified Cochran-Mantel-Haenszel
Point estimate	18.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	9.77
upper limit	26.59

Secondary: Percentage of participants with zero RBC units transfused over 24-Weeks

End point title	Percentage of participants with zero RBC units transfused over 24-Weeks ^[17]
End point description:	Percentage of participants with zero RBC units transfused over 24-weeks were reported.
End point type	Secondary
End point timeframe:	Up to 24 weeks

Notes:

[17] - 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 is only reporting on a subset of the arms that are contained in the Baseline period.

End point values	DAN 300 mg BID + Placebo	MMB 200 mg QD + Placebo		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	65 ^[18]	130 ^[19]		
Units: Percentage of participants				
number (confidence interval 95%)	16.92 (8.76 to 28.27)	35.38 (27.20 to 44.25)		

Notes:

[18] - ITT Analysis Set

[19] - ITT Analysis Set

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	DAN 300 mg BID + Placebo v MMB 200 mg QD + Placebo
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0012
Method	Cochran-Mantel-Haenszel
Parameter estimate	Stratified Cochran-Mantel-Haenszel
Point estimate	17.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.99
upper limit	26.4

Secondary: Percentage of participants with ≤4 RBC units transfused over 24-weeks

End point title	Percentage of participants with ≤4 RBC units transfused over 24-weeks ^[20]
End point description:	Percentage of participants with ≤4 RBC units transfused over 24-weeks were reported.
End point type	Secondary
End point timeframe:	Up to 24 weeks

Notes:

[20] - 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 is only reporting on a subset of the arms that are contained in the Baseline period.

End point values	DAN 300 mg BID + Placebo	MMB 200 mg QD + Placebo		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	65 ^[21]	130 ^[22]		
Units: Percentage of participants				
number (confidence interval 95%)	44.62 (32.27 to 57.47)	55.38 (46.42 to 64.10)		

Notes:

[21] - ITT Analysis Set

[22] - ITT Analysis Set

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	DAN 300 mg BID + Placebo v MMB 200 mg QD + Placebo

Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1133
Method	Cochran-Mantel-Haenszel
Parameter estimate	Stratified Cochran-Mantel-Haenszel
Point estimate	10.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.4
upper limit	23.64

Secondary: Duration of MFSAF TSS Response

End point title	Duration of MFSAF TSS Response ^[23]
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End point description:

Duration of MFSAF TSS response is defined as the number of days from the start of the initial 28-day period in which a participant had a $\geq 50\%$ reduction from Baseline TSS to the first day of the 7-day assessment that determines the mean TSS for the 28-day period during which the participants TSS equals or exceeds their Baseline value. Only those participants with data available at specified time point were analyzed. 99999 indicates $<25\%$ of participants experienced the event within the treatment arm. Hence, median and inter-quartile range could not be derived.

End point type	Secondary
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End point timeframe:

Up to a maximum of 77.6 weeks

Notes:

[23] - 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 is only reporting on a subset of the arms that are contained in the Baseline period.

End point values	DAN 300 mg BID + Placebo	MMB 200 mg QD + Placebo		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	6 ^[24]	32 ^[25]		
Units: Days				
median (inter-quartile range (Q1-Q3))	99999 (-99999 to 99999)	286.00 (286.00 to 286.00)		

Notes:

[24] - ITT Analysis Set

[25] - ITT Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Mean cumulative number of whole blood units transfused over 24 weeks

End point title	Mean cumulative number of whole blood units transfused over 24 weeks ^[26]
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End point description:

Cumulative transfusion risk was calculated as the estimated mean cumulative number of whole blood

units transfused during the study.

End point type	Secondary
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End point timeframe:

Up to Week 24

Notes:

[26] - 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 is only reporting on a subset of the arms that are contained in the Baseline period.

End point values	DAN 300 mg BID + Placebo	MMB 200 mg QD + Placebo		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	65 ^[27]	130 ^[28]		
Units: Whole blood units				
arithmetic mean (standard deviation)	10.86 (± 13.203)	6.55 (± 8.413)		

Notes:

[27] - ITT Analysis Set

[28] - ITT Analysis Set

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	DAN 300 mg BID + Placebo v MMB 200 mg QD + Placebo
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0006
Method	Anderson & Gill proportional means model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.556
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.397
upper limit	0.778

Secondary: Duration of TI response

End point title	Duration of TI response ^[29]
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End point description:

Duration of TI is defined as the number of days from (a) the first day of a 12-week period that satisfies the 12-week TI status definition, to (b) the first RBC transfusion or Hgb level < 8 g/dL (except in the case of clinically overt bleeding). Only those participants with data available at specified time point were analyzed. 99999 indicates <25% of participants experienced the event within the treatment arm. Hence, median and inter-quartile range could not be derived.

End point type	Secondary
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End point timeframe:

Up to a maximum of 77.6 weeks

Notes:

[29] - 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 is only reporting on a subset of the arms that are contained in the Baseline period.

End point values	DAN 300 mg BID + Placebo	MMB 200 mg QD + Placebo		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	13 ^[30]	39 ^[31]		
Units: Days				
median (inter-quartile range (Q1-Q3))	99999 (99999 to 99999)	99999 (99999 to 99999)		

Notes:

[30] - ITT Analysis Set

[31] - ITT Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with Transfusion Dependence (TD) status at Week 24

End point title	Percentage of participants with Transfusion Dependence (TD) status at Week 24 ^[32]
End point description:	TD status at Week 24 is defined as requirement of ≥ 4 RBC units in an 8-week period immediately prior to the end of Week 24.
End point type	Secondary
End point timeframe:	Week 24

Notes:

[32] - 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 is only reporting on a subset of the arms that are contained in the Baseline period.

End point values	DAN 300 mg BID + Placebo	MMB 200 mg QD + Placebo		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	65 ^[33]	130 ^[34]		
Units: Percentage of participants				
number (confidence interval 95%)	24.62 (14.77 to 36.87)	15.38 (9.66 to 22.76)		

Notes:

[33] - ITT Analysis Set

[34] - ITT Analysis Set

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	DAN 300 mg BID + Placebo v MMB 200 mg QD + Placebo

Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1602
Method	Cochran-Mantel-Haenszel
Parameter estimate	Stratified CMH
Point estimate	-8.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20.18
upper limit	3.66

Secondary: Percentage of participants with a hemoglobin response

End point title	Percentage of participants with a hemoglobin response ^[35]
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End point description:

Hemoglobin responses are defined as increases of ≥ 1 , ≥ 1.5 , or ≥ 2 g/dL from Baseline in Hgb, as measured over a (rolling) period of at least 12 consecutive weeks falling entirely before the end of Week 24. Baseline was the last assessment done before or on the day of first dose date. Data has been reported for percentage of participants who had ≥ 1 , ≥ 1.5 , or ≥ 2 g/dL increase from Baseline in hemoglobin.

End point type	Secondary
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End point timeframe:

Baseline and Week 24

Notes:

[35] - 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 is only reporting on a subset of the arms that are contained in the Baseline period.

End point values	DAN 300 mg BID + Placebo	MMB 200 mg QD + Placebo		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	65 ^[36]	130 ^[37]		
Units: Percentage of participants				
number (confidence interval 95%)				
≥ 1 g/dL Increase	33.85 (22.57 to 46.65)	53.08 (44.13 to 61.88)		
≥ 1.5 g/dL Increase	23.08 (13.53 to 35.19)	40.00 (31.51 to 48.95)		
≥ 2 g/dL Increase	20.00 (11.10 to 31.77)	29.23 (21.59 to 37.85)		

Notes:

[36] - ITT Analysis Set

[37] - ITT Analysis Set

Statistical analyses

Statistical analysis title	Statistical Analysis 1
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Statistical analysis description:

≥ 1 g/dL Increase in Hemoglobin response

Comparison groups	DAN 300 mg BID + Placebo v MMB 200 mg QD + Placebo
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Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0124
Method	Cochran-Mantel-Haenszel
Parameter estimate	Stratified CMH
Point estimate	19
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.68
upper limit	33.32

Statistical analysis title	Statistical Analysis 2
Statistical analysis description: >=1.5g/dL Increase in Hemoglobin response	
Comparison groups	DAN 300 mg BID + Placebo v MMB 200 mg QD + Placebo
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0282
Method	Cochran-Mantel-Haenszel
Parameter estimate	Stratified CMH
Point estimate	15.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.47
upper limit	28.9

Statistical analysis title	Statistical Analysis 3
Statistical analysis description: >=2g/dL Increase in Hemoglobin response	
Comparison groups	DAN 300 mg BID + Placebo v MMB 200 mg QD + Placebo
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2844
Method	Cochran-Mantel-Haenszel
Parameter estimate	Stratified CMH
Point estimate	6.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.41
upper limit	19.35

Secondary: Number of Baseline TD Participants With TI Status at Week 24

End point title	Number of Baseline TD Participants With TI Status at Week
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End point description:

Participants were defined as having TD if they met both of the following requirements in the 8 weeks immediately before the end of Week 24: ≥ 4 red blood cell or whole blood units were transfused (except in the case of clinically overt bleeding), each in response to a hemoglobin assessment of ≤ 9.5 g/dL; and there were ≥ 2 hemoglobin assessments with ≥ 28 days between the earliest and latest hemoglobin assessments. TI status was defined as not requiring red blood cell transfusion (except in the case of clinically overt bleeding) for ≥ 12 weeks immediately prior to the end of Week 24, with hemoglobin levels ≥ 8 g/dL. Only those participants with data available at specified time points were analyzed.

End point type	Secondary
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End point timeframe:

Week 24

Notes:

[38] - 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 is only reporting on a subset of the arms that are contained in the Baseline period.

End point values	DAN 300 mg BID + Placebo	MMB 200 mg QD + Placebo		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	34 ^[39]	63 ^[40]		
Units: Participants	3	9		

Notes:

[39] - ITT Analysis Set

[40] - ITT Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of TI in Baseline TD Participants

End point title	Duration of TI in Baseline TD Participants ^[41]
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End point description:

Duration of TI is defined as the number of days from (a) the first day of a 12-week period that satisfies the 12-week TI status definition, to (b) the first RBC transfusion or Hgb level < 8 g/dL (except in the case of clinically overt bleeding). Only those participants with data available at specified time points were analyzed. 99999 indicates $< 50\%$ of participants experienced the event within the treatment arm. Hence, median and third-quartile could not be derived.

End point type	Secondary
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End point timeframe:

Up to a maximum of 77.6 weeks

Notes:

[41] - 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 is only reporting on a subset of the arms that are contained in the Baseline period.

End point values	DAN 300 mg BID + Placebo	MMB 200 mg QD + Placebo		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	34 ^[42]	63 ^[43]		
Units: Days				
median (inter-quartile range (Q1-Q3))	99999 (196.0 to 99999)	99999 (224.0 to 99999)		

Notes:

[42] - ITT Analysis Set

[43] - ITT Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with serious adverse events (SAEs) and non-serious adverse events (non-SAEs)- up to Week 24

End point title	Number of participants with serious adverse events (SAEs) and non-serious adverse events (non-SAEs)- up to Week 24
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End point description:

An Adverse event (AE) is any untoward medical occurrence in a trial participant administered an investigational product(s), a comparator product, or an approved drug regardless of the causal relationship with treatment. An SAE is an AE that Results in death, life threatening, requires inpatient hospitalization or prolongation of an existing hospitalization, results in persistent or significant disability or incapacity, results in a congenital anomaly/birth defect or any important medical events as per medical or scientific judgment. Adverse events which were not Serious were considered as Non-Serious adverse events. Safety analysis set included all participants in the ITT Analysis set who received at least one dose of study drug.

End point type	Secondary
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End point timeframe:

Up to Week 24

End point values	MMB 200 mg QD + Placebo- Randomized DB TP	DAN 300 mg BID + Placebo- Randomized DB TP		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	130 ^[44]	65 ^[45]		
Units: Participants				
Any non-SAEs	108	55		
Any SAEs	45	26		

Notes:

[44] - Safety analysis set

[45] - Safety analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with serious adverse events (SAEs) and non-serious adverse events (non-SAEs)- From Week 24 to Week 204

End point title	Number of participants with serious adverse events (SAEs) and non-serious adverse events (non-SAEs)- From Week 24 to Week 204
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End point description:

An AE is any untoward medical occurrence in a trial participant administered an investigational product(s), a comparator product, or an approved drug regardless of the causal relationship with treatment. An SAE is an AE that Results in death, life threatening, requires inpatient hospitalization or prolongation of an existing hospitalization, results in persistent or significant disability or incapacity, results in a congenital anomaly/birth defect or any important medical events as per medical or scientific judgment. Adverse events which were not Serious were considered as Non-Serious adverse events.

End point type Secondary

End point timeframe:

From Week 24 to Week 204

End point values	MMB 200 mg QD- Open-Label Extended TP	DAN 300 mg BID to MMB 200 mg QD- Open-Label Extended TP		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	93 ^[46]	41 ^[47]		
Units: Participants				
Any non-SAEs	57	28		
Any SAEs	30	12		

Notes:

[46] - Safety analysis set

[47] - Safety analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Leukemia-free Survival (LFS)

End point title Leukemia-free Survival (LFS)^[48]

End point description:

LFS is defined as the interval from first study drug dosing date (or randomization date for participants who did not receive treatment) to any evidence of leukemic transformation and/or death (from any cause). Values are presented based on the Kaplan-Meier analysis. All participants (overall population) were included in analysis. 99999 indicates <50% of participants experienced the event within the treatment arm. Hence, median and third-quartile could not be derived and 88888 indicates <75% of participants experienced the event within the treatment arm. Hence, third-quartile could not be derived.

End point type Secondary

End point timeframe:

Up to a maximum of 77.6 weeks

Notes:

[48] - 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 is only reporting on a subset of the arms that are contained in the Baseline period.

End point values	DAN 300 mg BID + Placebo	MMB 200 mg QD + Placebo		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	65 ^[49]	130 ^[50]		
Units: Days				
median (inter-quartile range (Q1-Q3))	99999 (284.0 to 99999)	624.0 (325.0 to 88888)		

Notes:

[49] - ITT Analysis Set

[50] - ITT Analysis Set

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	DAN 300 mg BID + Placebo v MMB 200 mg QD + Placebo
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.432
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.804
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.466
upper limit	1.386

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS) ^[51]
End point description:	Overall survival is defined as the interval from the first study drug dosing date (or randomization date for participants who did not receive treatment) to death from any cause. Values are presented based on the Kaplan-Meier analysis. All participants (overall population) were included in analysis. 99999 indicates <50% of participants experienced the event within the treatment arm. Hence, median and third-quartile could not be derived and 88888 indicates <75% of participants experienced the event within the treatment arm. Hence, third-quartile could not be derived.
End point type	Secondary
End point timeframe:	Up to a maximum of 77.6 weeks

Notes:

[51] - 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 is only reporting on a subset of the arms that are contained in the Baseline period.

End point values	DAN 300 mg BID + Placebo	MMB 200 mg QD + Placebo		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	65 ^[52]	130 ^[53]		
Units: Days				
median (inter-quartile range (Q1-Q3))	99999 (309.00 to 99999)	624.0 (333.0 to 88888)		

Notes:

[52] - ITT Analysis Set

[53] - ITT Analysis Set

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	DAN 300 mg BID + Placebo v MMB 200 mg QD + Placebo
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6879
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.504
upper limit	1.572

Secondary: Change From Baseline in Disease-related Fatigue as Assessed by MFSAF TSS v4.0 at Week 24

End point title	Change From Baseline in Disease-related Fatigue as Assessed by MFSAF TSS v4.0 at Week 24 ^[54]
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End point description:

The MFSAF v4.0 comprises 7 domains representing the 7 most relevant symptoms of MF identified through existing participant- and clinician-based evidence: fatigue, night sweats, pruritus, abdominal discomfort, pain under the left ribs, early satiety, and bone pain. Participants scored each symptom domain using an 11-point numeric rating scale ranging from 0 (absent) to 10 (worst imaginable). The total possible range of scores was 0 to 70, with higher scores corresponding to more severe MF symptoms. An increase in score from Baseline indicated a worsening of MF symptoms, and a decrease in score from Baseline indicated an improvement in MF symptoms. Baseline was the last assessment done before or on the day of first dose date. Change from Baseline was defined as the post-Baseline value minus Baseline value. Only those participants with data available at specified time points were analyzed.

End point type	Secondary
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End point timeframe:

Baseline and Week 24

Notes:

[54] - 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 is only reporting on a subset of the arms that are contained in the Baseline period.

End point values	DAN 300 mg BID + Placebo	MMB 200 mg QD + Placebo		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	37 ^[55]	92 ^[56]		
Units: Scores on a scale				
least squares mean (standard error)	-0.82 (± 0.31)	-1.53 (± 0.20)		

Notes:

[55] - ITT Analysis Set

[56] - ITT Analysis Set

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	DAN 300 mg BID + Placebo v MMB 200 mg QD + Placebo
Number of subjects included in analysis	129
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0513
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.42
upper limit	0

Secondary: Change From Baseline in Cancer-related Fatigue as Assessed by European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) at Week 24

End point title	Change From Baseline in Cancer-related Fatigue as Assessed by European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) at Week 24 ^[57]
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End point description:

The EORTC QLQ-C30 is comprised of 5 functional scales (physical, role, emotional, social, cognitive), eight single item symptom scales (fatigue, pain, nausea/vomiting, appetite loss, constipation, diarrhea, insomnia, dyspnea), as well as sub-scales assessing global health/quality of life and financial impact. Most items use a 4-point Likert scale from "not at all" to "very much" and a one-week recall period with the exception of the final two items which use a 7 point scale response from "very poor" to "excellent". Scores were averaged and transformed to a 0-100 scale, with higher scores representing better functioning/quality of life. An increase in scores from Baseline indicated an improved functioning/quality of life, and a decrease in scores from Baseline indicated a worsened functioning/quality of life. Baseline was the last assessment done before or on the day of first dose date. Change from Baseline was defined as the post-Baseline value minus Baseline value.

End point type	Secondary
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End point timeframe:

Baseline and Week 24

Notes:

[57] - 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 is only reporting on a subset of the arms that are contained in the Baseline period.

End point values	DAN 300 mg BID + Placebo	MMB 200 mg QD + Placebo		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	35 ^[58]	89 ^[59]		
Units: Scores on a scale				
least squares mean (standard error)	-3.52 (± 3.65)	-14.34 (± 2.35)		

Notes:

[58] - ITT Analysis Set. Only those participants with data available at specified time points were analyzed

[59] - ITT Analysis Set. Only those participants with data available at specified time points were analyzed

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	DAN 300 mg BID + Placebo v MMB 200 mg QD + Placebo
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0113
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	-10.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.15
upper limit	-2.48

Secondary: Change From Baseline in Physical Function Score as Assessed by Patient-Reported Outcomes Measurement Information System (PROMIS) Physical Function Short Form 10b at Week 24

End point title	Change From Baseline in Physical Function Score as Assessed by Patient-Reported Outcomes Measurement Information System (PROMIS) Physical Function Short Form 10b at Week 24 ^[60]
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End point description:

PROMIS Physical Function Short Form 10b consists of 14 questions; each with a 5-point response. PROMIS short form assesses self-reported capability of a participant rather than actual performance of physical activities. This includes functioning of one's upper extremities (dexterity), lower extremities (walking or mobility), and central regions (neck, back) as well as instrumental activities of daily living, such as running errands. Participants scored each response on a scale from 1 (unable to do) to 5 (without any difficulty, or not at all). Total possible range of scores was 14 to 70, with higher scores corresponding to a greater physical function ability. An increase in score from Baseline indicated an improvement in physical function ability and a decrease in score from Baseline indicated a reduction in physical function ability. Baseline was last assessment done before or on the day of first dose date. Change from Baseline was defined as post-Baseline value minus Baseline value

End point type	Secondary
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End point timeframe:

Baseline and Week 24

Notes:

[60] - 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 is only reporting on a subset of the arms that are contained in the Baseline period.

End point values	DAN 300 mg BID + Placebo	MMB 200 mg QD + Placebo		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	32 ^[61]	89 ^[62]		
Units: Scores on a scale				
least squares mean (standard error)	-0.11 (± 1.21)	1.19 (± 0.77)		

Notes:

[61] - ITT Analysis Set. Only those participants with data available at specified time points were analyzed

[62] - ITT Analysis Set. Only those participants with data available at specified time points were analyzed

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	DAN 300 mg BID + Placebo v MMB 200 mg QD + Placebo
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.357
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	1.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.49
upper limit	4.11

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All-cause mortality, Serious adverse events (SAEs) and non-SAEs were collected up to Week 24 for Randomized Double-Blind Treatment Period and From Week 24 to a maximum of 77.6 weeks for the Open-Label Extended Treatment Period

Adverse event reporting additional description:

Serious adverse events (SAEs) and non-SAEs were measured in the Safety analysis set, which included all participants in the ITT analysis set who received at least one dose of study drug.

All-cause mortality was measured in the ITT analysis set, which included all randomized participants. Data are presented per treatment received.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	24.0
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Reporting groups

Reporting group title	MMB 200 mg QD + Placebo- Randomized DB TP
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Reporting group description:

Participants were randomized to receive 200 mg of MMB orally QD and a DAN-placebo orally BID during the randomized 24-week double-blind treatment period.

Reporting group title	DAN 300 mg BID to MMB 200 mg QD- Open-Label Extended TP
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Reporting group description:

Participants who completed the randomized treatment period, discontinued treatment early due to splenic progression, or discontinued treatment early for other reasons but completed scheduled assessments through Week 24 were enrolled in an open-label extended treatment period. Participants who received DAN 300 mg BID during randomized period switched to receive 200 mg of MMB orally QD during open-label extended treatment period.

Reporting group title	MMB 200 mg QD- Open-Label Extended TP
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Reporting group description:

Participants who completed the randomized treatment period or discontinued treatment early for other reasons but completed scheduled assessments through Week 24 were enrolled in an open-label extended treatment period. Participants continued to receive 200 mg of MMB orally QD during the open-label extended treatment period.

Reporting group title	DAN 300 mg BID + Placebo- Randomized DB TP
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Reporting group description:

Participants were randomized to receive 300 mg of DAN orally BID and MMB-placebo orally QD during the randomized 24-week double-blind treatment period.

Serious adverse events	MMB 200 mg QD + Placebo- Randomized DB TP	DAN 300 mg BID to MMB 200 mg QD- Open-Label Extended TP	MMB 200 mg QD- Open-Label Extended TP
Total subjects affected by serious adverse events			
subjects affected / exposed	45 / 130 (34.62%)	12 / 41 (29.27%)	30 / 93 (32.26%)
number of deaths (all causes)	25	8	23
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			

subjects affected / exposed	1 / 130 (0.77%)	0 / 41 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Leukaemia cutis			
subjects affected / exposed	0 / 130 (0.00%)	0 / 41 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastatic malignant melanoma			
subjects affected / exposed	1 / 130 (0.77%)	0 / 41 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tongue neoplasm malignant stage unspecified			
subjects affected / exposed	1 / 130 (0.77%)	0 / 41 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transformation to acute myeloid leukaemia			
subjects affected / exposed	3 / 130 (2.31%)	1 / 41 (2.44%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 1	0 / 0
Adenocarcinoma			
subjects affected / exposed	0 / 130 (0.00%)	1 / 41 (2.44%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Basal cell carcinoma			
subjects affected / exposed	0 / 130 (0.00%)	1 / 41 (2.44%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 130 (0.00%)	0 / 41 (0.00%)	2 / 93 (2.15%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			

Aortic stenosis			
subjects affected / exposed	0 / 130 (0.00%)	0 / 41 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Shock haemorrhagic			
subjects affected / exposed	1 / 130 (0.77%)	0 / 41 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	1 / 130 (0.77%)	0 / 41 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Circulatory collapse			
subjects affected / exposed	1 / 130 (0.77%)	0 / 41 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Haematoma			
subjects affected / exposed	0 / 130 (0.00%)	1 / 41 (2.44%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 130 (0.00%)	0 / 41 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disease progression			
subjects affected / exposed	0 / 130 (0.00%)	0 / 41 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden death			
subjects affected / exposed	1 / 130 (0.77%)	1 / 41 (2.44%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0

Pyrexia			
subjects affected / exposed	3 / 130 (2.31%)	1 / 41 (2.44%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	1 / 130 (0.77%)	0 / 41 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	2 / 130 (1.54%)	0 / 41 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Death			
subjects affected / exposed	0 / 130 (0.00%)	0 / 41 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 130 (0.00%)	0 / 41 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Complication associated with device			
subjects affected / exposed	0 / 130 (0.00%)	1 / 41 (2.44%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 130 (0.77%)	0 / 41 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Prostatitis			
subjects affected / exposed	1 / 130 (0.77%)	0 / 41 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	1 / 130 (0.77%)	0 / 41 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	1 / 130 (0.77%)	1 / 41 (2.44%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	1 / 130 (0.77%)	0 / 41 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 130 (0.77%)	0 / 41 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Restrictive pulmonary disease			
subjects affected / exposed	0 / 130 (0.00%)	0 / 41 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	0 / 130 (0.00%)	1 / 41 (2.44%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary arterial hypertension			
subjects affected / exposed	0 / 130 (0.00%)	0 / 41 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute respiratory failure			
subjects affected / exposed	0 / 130 (0.00%)	1 / 41 (2.44%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Psychiatric disorders			
Delirium			
subjects affected / exposed	1 / 130 (0.77%)	0 / 41 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	0 / 130 (0.00%)	0 / 41 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Personality change			
subjects affected / exposed	0 / 130 (0.00%)	1 / 41 (2.44%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
General physical condition abnormal			
subjects affected / exposed	1 / 130 (0.77%)	0 / 41 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver function test increased			
subjects affected / exposed	0 / 130 (0.00%)	0 / 41 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 130 (0.77%)	0 / 41 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	0 / 130 (0.00%)	0 / 41 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma			

subjects affected / exposed	0 / 130 (0.00%)	1 / 41 (2.44%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervical vertebral fracture			
subjects affected / exposed	1 / 130 (0.77%)	0 / 41 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	0 / 130 (0.00%)	0 / 41 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower limb fracture			
subjects affected / exposed	0 / 130 (0.00%)	0 / 41 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Periprosthetic fracture			
subjects affected / exposed	0 / 130 (0.00%)	0 / 41 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 130 (0.77%)	1 / 41 (2.44%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery stenosis			
subjects affected / exposed	0 / 130 (0.00%)	0 / 41 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	0 / 130 (0.00%)	0 / 41 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiogenic shock			

subjects affected / exposed	0 / 130 (0.00%)	0 / 41 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	2 / 130 (1.54%)	0 / 41 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	1 / 130 (0.77%)	0 / 41 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	0 / 130 (0.00%)	1 / 41 (2.44%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Atrial thrombosis			
subjects affected / exposed	0 / 130 (0.00%)	1 / 41 (2.44%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arrhythmia			
subjects affected / exposed	0 / 130 (0.00%)	0 / 41 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cardiac failure chronic			
subjects affected / exposed	0 / 130 (0.00%)	0 / 41 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	0 / 130 (0.00%)	0 / 41 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			

subjects affected / exposed	0 / 130 (0.00%)	0 / 41 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia			
subjects affected / exposed	0 / 130 (0.00%)	1 / 41 (2.44%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 130 (0.00%)	0 / 41 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 130 (0.77%)	0 / 41 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 130 (0.00%)	0 / 41 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	3 / 130 (2.31%)	0 / 41 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral haemorrhage			
subjects affected / exposed	0 / 130 (0.00%)	0 / 41 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 130 (3.85%)	1 / 41 (2.44%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	1 / 5	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Blood loss anaemia			

subjects affected / exposed	0 / 130 (0.00%)	0 / 41 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	1 / 130 (0.77%)	0 / 41 (0.00%)	2 / 93 (2.15%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	3 / 130 (2.31%)	0 / 41 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	2 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Splenic vein thrombosis			
subjects affected / exposed	1 / 130 (0.77%)	0 / 41 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Splenic infarction			
subjects affected / exposed	1 / 130 (0.77%)	0 / 41 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Splenic haematoma			
subjects affected / exposed	1 / 130 (0.77%)	0 / 41 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastric ulcer perforation			
subjects affected / exposed	1 / 130 (0.77%)	0 / 41 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematochezia			
subjects affected / exposed	1 / 130 (0.77%)	0 / 41 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Melaena			

subjects affected / exposed	1 / 130 (0.77%)	0 / 41 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	1 / 130 (0.77%)	0 / 41 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoperitoneum			
subjects affected / exposed	1 / 130 (0.77%)	0 / 41 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 130 (0.77%)	0 / 41 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Oesophageal varices haemorrhage			
subjects affected / exposed	1 / 130 (0.77%)	0 / 41 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic erosive gastritis			
subjects affected / exposed	0 / 130 (0.00%)	0 / 41 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enteritis			
subjects affected / exposed	0 / 130 (0.00%)	0 / 41 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholangitis acute			
subjects affected / exposed	1 / 130 (0.77%)	0 / 41 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			

subjects affected / exposed	1 / 130 (0.77%)	0 / 41 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatotoxicity			
subjects affected / exposed	0 / 130 (0.00%)	0 / 41 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis			
subjects affected / exposed	1 / 130 (0.77%)	0 / 41 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Chronic kidney disease			
subjects affected / exposed	0 / 130 (0.00%)	0 / 41 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute kidney injury			
subjects affected / exposed	4 / 130 (3.08%)	2 / 41 (4.88%)	2 / 93 (2.15%)
occurrences causally related to treatment / all	0 / 6	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	2 / 130 (1.54%)	0 / 41 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	0 / 130 (0.00%)	0 / 41 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Tenosynovitis			

subjects affected / exposed	1 / 130 (0.77%)	0 / 41 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sarcopenia			
subjects affected / exposed	0 / 130 (0.00%)	0 / 41 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Clostridium difficile colitis			
subjects affected / exposed	1 / 130 (0.77%)	0 / 41 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	2 / 130 (1.54%)	0 / 41 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Biliary sepsis			
subjects affected / exposed	1 / 130 (0.77%)	0 / 41 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	1 / 130 (0.77%)	0 / 41 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19			
subjects affected / exposed	3 / 130 (2.31%)	0 / 41 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 0
COVID-19 pneumonia			
subjects affected / exposed	3 / 130 (2.31%)	0 / 41 (0.00%)	4 / 93 (4.30%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 0
Cystitis			

subjects affected / exposed	1 / 130 (0.77%)	0 / 41 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint abscess			
subjects affected / exposed	1 / 130 (0.77%)	0 / 41 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterococcal sepsis			
subjects affected / exposed	0 / 130 (0.00%)	0 / 41 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	1 / 130 (0.77%)	0 / 41 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pyelonephritis acute			
subjects affected / exposed	0 / 130 (0.00%)	0 / 41 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	3 / 130 (2.31%)	1 / 41 (2.44%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Listeria sepsis			
subjects affected / exposed	1 / 130 (0.77%)	0 / 41 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia sepsis			
subjects affected / exposed	0 / 130 (0.00%)	0 / 41 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal sepsis			

subjects affected / exposed	0 / 130 (0.00%)	0 / 41 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Streptococcal bacteraemia			
subjects affected / exposed	1 / 130 (0.77%)	0 / 41 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tooth abscess			
subjects affected / exposed	1 / 130 (0.77%)	0 / 41 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	2 / 130 (1.54%)	1 / 41 (2.44%)	2 / 93 (2.15%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abscess limb			
subjects affected / exposed	0 / 130 (0.00%)	0 / 41 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis rotavirus			
subjects affected / exposed	0 / 130 (0.00%)	0 / 41 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Escherichia infection			
subjects affected / exposed	0 / 130 (0.00%)	0 / 41 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Enterobacter sepsis			
subjects affected / exposed	0 / 130 (0.00%)	1 / 41 (2.44%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Endocarditis			

subjects affected / exposed	0 / 130 (0.00%)	0 / 41 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	0 / 130 (0.00%)	0 / 41 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Periorbital cellulitis			
subjects affected / exposed	0 / 130 (0.00%)	0 / 41 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia bacterial			
subjects affected / exposed	0 / 130 (0.00%)	0 / 41 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia influenzal			
subjects affected / exposed	0 / 130 (0.00%)	0 / 41 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia staphylococcal			
subjects affected / exposed	0 / 130 (0.00%)	0 / 41 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Splenic abscess			
subjects affected / exposed	0 / 130 (0.00%)	0 / 41 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Urosepsis			
subjects affected / exposed	0 / 130 (0.00%)	0 / 41 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pulmonary sepsis			

subjects affected / exposed	0 / 130 (0.00%)	0 / 41 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Fluid overload			
subjects affected / exposed	2 / 130 (1.54%)	0 / 41 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	1 / 130 (0.77%)	1 / 41 (2.44%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	0 / 130 (0.00%)	0 / 41 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Decreased appetite			
subjects affected / exposed	0 / 130 (0.00%)	1 / 41 (2.44%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	DAN 300 mg BID + Placebo- Randomized DB TP		
Total subjects affected by serious adverse events			
subjects affected / exposed	26 / 65 (40.00%)		
number of deaths (all causes)	16		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	1 / 65 (1.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Leukaemia cutis			

subjects affected / exposed	1 / 65 (1.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metastatic malignant melanoma			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tongue neoplasm malignant stage unspecified			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Transformation to acute myeloid leukaemia			
subjects affected / exposed	2 / 65 (3.08%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Adenocarcinoma			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Basal cell carcinoma			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	1 / 65 (1.54%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Shock haemorrhagic			

subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypotension			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Circulatory collapse			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haematoma			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 65 (1.54%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Disease progression			
subjects affected / exposed	1 / 65 (1.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Sudden death			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Oedema peripheral			

subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General physical health deterioration			
subjects affected / exposed	2 / 65 (3.08%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Death			
subjects affected / exposed	1 / 65 (1.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Complication associated with device			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Prostatitis			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			

subjects affected / exposed	1 / 65 (1.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia aspiration			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Restrictive pulmonary disease			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pulmonary oedema			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pulmonary arterial hypertension			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Acute respiratory failure			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Delirium			

subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Depression			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Personality change			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Investigations			
General physical condition abnormal			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Liver function test increased			
subjects affected / exposed	1 / 65 (1.54%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	1 / 65 (1.54%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Subdural haematoma			
subjects affected / exposed	1 / 65 (1.54%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		

Cervical vertebral fracture			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Fall			
subjects affected / exposed	1 / 65 (1.54%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Lower limb fracture			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Periprosthetic fracture			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Coronary artery stenosis			
subjects affected / exposed	1 / 65 (1.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Coronary artery disease			
subjects affected / exposed	1 / 65 (1.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiogenic shock			
subjects affected / exposed	1 / 65 (1.54%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Atrial fibrillation			

subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Myocardial ischaemia			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac arrest			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Atrial thrombosis			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Arrhythmia			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac failure chronic			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac failure			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac failure congestive			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tachycardia			

subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Myocardial infarction			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 65 (1.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 65 (1.54%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cerebral haemorrhage			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 65 (4.62%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 3		
Blood loss anaemia			
subjects affected / exposed	1 / 65 (1.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			

subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Splenic vein thrombosis			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Splenic infarction			
subjects affected / exposed	2 / 65 (3.08%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Splenic haematoma			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Gastric ulcer perforation			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haematochezia			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Melaena			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Small intestinal obstruction			

subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haemoperitoneum			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Oesophageal varices haemorrhage			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haemorrhagic erosive gastritis			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Enteritis			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholangitis acute			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholecystitis acute			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatotoxicity			

subjects affected / exposed	1 / 65 (1.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatitis			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Chronic kidney disease			
subjects affected / exposed	1 / 65 (1.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Acute kidney injury			
subjects affected / exposed	3 / 65 (4.62%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Renal failure			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	1 / 65 (1.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Tenosynovitis			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sarcopenia			

subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Clostridium difficile colitis			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	1 / 65 (1.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Biliary sepsis			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bronchitis			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
COVID-19			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
COVID-19 pneumonia			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cystitis			
subjects affected / exposed	1 / 65 (1.54%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Joint abscess			

subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Enterococcal sepsis			
subjects affected / exposed	1 / 65 (1.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Septic shock			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis acute			
subjects affected / exposed	1 / 65 (1.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	6 / 65 (9.23%)		
occurrences causally related to treatment / all	2 / 6		
deaths causally related to treatment / all	0 / 0		
Listeria sepsis			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Escherichia sepsis			
subjects affected / exposed	1 / 65 (1.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Staphylococcal sepsis			
subjects affected / exposed	1 / 65 (1.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Streptococcal bacteraemia			

subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tooth abscess			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Abscess limb			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis rotavirus			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Escherichia infection			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Enterobacter sepsis			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endocarditis			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infective exacerbation of chronic obstructive airways disease			

subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Periorbital cellulitis			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia bacterial			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia influenzal			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia staphylococcal			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Splenic abscess			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urosepsis			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pulmonary sepsis			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Fluid overload			

subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyperkalaemia			
subjects affected / exposed	1 / 65 (1.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypoglycaemia			
subjects affected / exposed	1 / 65 (1.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Decreased appetite			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	MMB 200 mg QD + Placebo- Randomized DB TP	DAN 300 mg BID to MMB 200 mg QD- Open-Label Extended TP	MMB 200 mg QD- Open-Label Extended TP
Total subjects affected by non-serious adverse events			
subjects affected / exposed	108 / 130 (83.08%)	28 / 41 (68.29%)	57 / 93 (61.29%)
Vascular disorders			
Hypertension			
subjects affected / exposed	6 / 130 (4.62%)	5 / 41 (12.20%)	3 / 93 (3.23%)
occurrences (all)	6	5	3
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	8 / 130 (6.15%)	3 / 41 (7.32%)	6 / 93 (6.45%)
occurrences (all)	10	3	11
Oedema peripheral			
subjects affected / exposed	9 / 130 (6.92%)	1 / 41 (2.44%)	3 / 93 (3.23%)
occurrences (all)	9	1	3
Pyrexia			

subjects affected / exposed occurrences (all)	11 / 130 (8.46%) 13	3 / 41 (7.32%) 4	12 / 93 (12.90%) 13
Asthenia subjects affected / exposed occurrences (all)	17 / 130 (13.08%) 20	0 / 41 (0.00%) 0	12 / 93 (12.90%) 15
Respiratory, thoracic and mediastinal disorders			
Dyspnoea subjects affected / exposed occurrences (all)	9 / 130 (6.92%) 10	0 / 41 (0.00%) 0	7 / 93 (7.53%) 8
Epistaxis subjects affected / exposed occurrences (all)	7 / 130 (5.38%) 7	3 / 41 (7.32%) 3	1 / 93 (1.08%) 2
Cough subjects affected / exposed occurrences (all)	9 / 130 (6.92%) 10	2 / 41 (4.88%) 2	8 / 93 (8.60%) 9
Investigations			
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	9 / 130 (6.92%) 13	1 / 41 (2.44%) 1	2 / 93 (2.15%) 4
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	7 / 130 (5.38%) 9	1 / 41 (2.44%) 1	3 / 93 (3.23%) 3
Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	10 / 130 (7.69%) 18	1 / 41 (2.44%) 1	3 / 93 (3.23%) 3
Weight decreased subjects affected / exposed occurrences (all)	14 / 130 (10.77%) 16	7 / 41 (17.07%) 7	9 / 93 (9.68%) 9
Platelet count decreased subjects affected / exposed occurrences (all)	9 / 130 (6.92%) 24	1 / 41 (2.44%) 2	3 / 93 (3.23%) 7
Blood creatinine increased subjects affected / exposed occurrences (all)	10 / 130 (7.69%) 18	4 / 41 (9.76%) 4	7 / 93 (7.53%) 13
Injury, poisoning and procedural complications			

Fall subjects affected / exposed occurrences (all)	7 / 130 (5.38%) 9	0 / 41 (0.00%) 0	4 / 93 (4.30%) 6
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	8 / 130 (6.15%) 9	4 / 41 (9.76%) 4	1 / 93 (1.08%) 1
Paraesthesia subjects affected / exposed occurrences (all)	8 / 130 (6.15%) 10	0 / 41 (0.00%) 0	1 / 93 (1.08%) 1
Blood and lymphatic system disorders Neutropenia subjects affected / exposed occurrences (all)	7 / 130 (5.38%) 11	2 / 41 (4.88%) 2	5 / 93 (5.38%) 9
Anaemia subjects affected / exposed occurrences (all)	12 / 130 (9.23%) 34	3 / 41 (7.32%) 6	9 / 93 (9.68%) 18
Thrombocytopenia subjects affected / exposed occurrences (all)	28 / 130 (21.54%) 50	7 / 41 (17.07%) 10	13 / 93 (13.98%) 22
Gastrointestinal disorders Abdominal pain upper subjects affected / exposed occurrences (all)	3 / 130 (2.31%) 3	1 / 41 (2.44%) 1	2 / 93 (2.15%) 3
Abdominal pain subjects affected / exposed occurrences (all)	10 / 130 (7.69%) 12	1 / 41 (2.44%) 2	3 / 93 (3.23%) 3
Vomiting subjects affected / exposed occurrences (all)	9 / 130 (6.92%) 10	1 / 41 (2.44%) 1	3 / 93 (3.23%) 3
Nausea subjects affected / exposed occurrences (all)	21 / 130 (16.15%) 28	0 / 41 (0.00%) 0	8 / 93 (8.60%) 10
Diarrhoea subjects affected / exposed occurrences (all)	29 / 130 (22.31%) 40	5 / 41 (12.20%) 7	16 / 93 (17.20%) 21
Constipation			

subjects affected / exposed occurrences (all)	11 / 130 (8.46%) 13	2 / 41 (4.88%) 2	4 / 93 (4.30%) 4
Skin and subcutaneous tissue disorders			
Night sweats			
subjects affected / exposed	4 / 130 (3.08%)	0 / 41 (0.00%)	2 / 93 (2.15%)
occurrences (all)	4	0	2
Rash			
subjects affected / exposed	3 / 130 (2.31%)	0 / 41 (0.00%)	0 / 93 (0.00%)
occurrences (all)	3	0	0
Pruritus			
subjects affected / exposed	13 / 130 (10.00%)	1 / 41 (2.44%)	6 / 93 (6.45%)
occurrences (all)	14	1	7
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 130 (1.54%)	1 / 41 (2.44%)	1 / 93 (1.08%)
occurrences (all)	2	1	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 130 (3.08%)	3 / 41 (7.32%)	1 / 93 (1.08%)
occurrences (all)	5	4	1
Infections and infestations			
COVID-19			
subjects affected / exposed	9 / 130 (6.92%)	0 / 41 (0.00%)	8 / 93 (8.60%)
occurrences (all)	9	0	8
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	9 / 130 (6.92%)	1 / 41 (2.44%)	4 / 93 (4.30%)
occurrences (all)	13	1	5
Hyperkalaemia			
subjects affected / exposed	6 / 130 (4.62%)	2 / 41 (4.88%)	2 / 93 (2.15%)
occurrences (all)	7	2	3
Hyperuricaemia			
subjects affected / exposed	9 / 130 (6.92%)	3 / 41 (7.32%)	3 / 93 (3.23%)
occurrences (all)	9	3	3
Hyponatraemia			

subjects affected / exposed	3 / 130 (2.31%)	0 / 41 (0.00%)	3 / 93 (3.23%)
occurrences (all)	5	0	3

Non-serious adverse events	DAN 300 mg BID + Placebo- Randomized DB TP		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	55 / 65 (84.62%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	6 / 65 (9.23%)		
occurrences (all)	6		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	6 / 65 (9.23%)		
occurrences (all)	10		
Oedema peripheral			
subjects affected / exposed	9 / 65 (13.85%)		
occurrences (all)	10		
Pyrexia			
subjects affected / exposed	5 / 65 (7.69%)		
occurrences (all)	6		
Asthenia			
subjects affected / exposed	6 / 65 (9.23%)		
occurrences (all)	8		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	10 / 65 (15.38%)		
occurrences (all)	12		
Epistaxis			
subjects affected / exposed	4 / 65 (6.15%)		
occurrences (all)	6		
Cough			
subjects affected / exposed	2 / 65 (3.08%)		
occurrences (all)	2		
Investigations			

Alanine aminotransferase increased subjects affected / exposed occurrences (all)	5 / 65 (7.69%) 11		
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	4 / 65 (6.15%) 5		
Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	0 / 65 (0.00%) 0		
Weight decreased subjects affected / exposed occurrences (all)	3 / 65 (4.62%) 4		
Platelet count decreased subjects affected / exposed occurrences (all)	3 / 65 (4.62%) 4		
Blood creatinine increased subjects affected / exposed occurrences (all)	10 / 65 (15.38%) 16		
Injury, poisoning and procedural complications Fall subjects affected / exposed occurrences (all)	3 / 65 (4.62%) 3		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Paraesthesia subjects affected / exposed occurrences (all)	1 / 65 (1.54%) 1 1 / 65 (1.54%) 1		
Blood and lymphatic system disorders Neutropenia subjects affected / exposed occurrences (all) Anaemia subjects affected / exposed occurrences (all)	2 / 65 (3.08%) 5 6 / 65 (9.23%) 11		

Thrombocytopenia subjects affected / exposed occurrences (all)	7 / 65 (10.77%) 11		
Gastrointestinal disorders			
Abdominal pain upper subjects affected / exposed occurrences (all)	5 / 65 (7.69%) 6		
Abdominal pain subjects affected / exposed occurrences (all)	6 / 65 (9.23%) 6		
Vomiting subjects affected / exposed occurrences (all)	0 / 65 (0.00%) 0		
Nausea subjects affected / exposed occurrences (all)	6 / 65 (9.23%) 6		
Diarrhoea subjects affected / exposed occurrences (all)	6 / 65 (9.23%) 7		
Constipation subjects affected / exposed occurrences (all)	5 / 65 (7.69%) 5		
Skin and subcutaneous tissue disorders			
Night sweats subjects affected / exposed occurrences (all)	4 / 65 (6.15%) 5		
Rash subjects affected / exposed occurrences (all)	4 / 65 (6.15%) 4		
Pruritus subjects affected / exposed occurrences (all)	7 / 65 (10.77%) 7		
Renal and urinary disorders			
Acute kidney injury subjects affected / exposed occurrences (all)	5 / 65 (7.69%) 5		
Musculoskeletal and connective tissue			

disorders			
Arthralgia			
subjects affected / exposed	2 / 65 (3.08%)		
occurrences (all)	3		
Infections and infestations			
COVID-19			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences (all)	0		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	6 / 65 (9.23%)		
occurrences (all)	8		
Hyperkalaemia			
subjects affected / exposed	6 / 65 (9.23%)		
occurrences (all)	12		
Hyperuricaemia			
subjects affected / exposed	4 / 65 (6.15%)		
occurrences (all)	6		
Hyponatraemia			
subjects affected / exposed	4 / 65 (6.15%)		
occurrences (all)	4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 August 2019	Protocol Amendment 1: <ul style="list-style-type: none">• Clarified criteria for dose reduction due to thrombocytopenia, neutropenia, and nonhematologic or other toxicities; and subsequent dose re-escalation.• Modified thresholds for platelet count recovery required to resume treatment based on Baseline value.• Updated procedures for managing transition from randomized treatment to open-label treatment so treatment assignment would only be unblinded when required to determine eligibility for open-label treatment with MMB or DAN.
18 December 2020	Protocol Amendment 2: <ul style="list-style-type: none">• Removed interim analysis for sample size reassessment from the study design.• Modified the planned statistical analysis: Moved the MMRM analysis of the MFSAF TSS secondary endpoint to the fourth position in the overall statistical testing hierarchy. – Revised description of the hierarchical statistical testing of secondary endpoints. Updated descriptions of the secondary endpoints. Updated statistics section.• Changed timing of first dose after randomization, JAK inhibitor nontreatment period, exclusion of active anti-MF medication, and Baseline spleen volume assessment to allow flexibility for scheduling randomization and day 1.• Inclusion criteria were modified: Criterion 3: clarified that an MFSAF TSS of ≥ 10 units was required during screening prior to Baseline day 1. Criteria 4a and 4c: clarified the definition of anemic. – Criterion 5b: added that participants receiving a low dose of a JAK inhibitor could have a reduced taper period, or no taper, with sponsor approval. Criterion 9: clarified that platelet count must be met without requirement for platelet transfusion.• Exclusion criteria were modified: Criterion 1b: clarified that approved JAK inhibitors were prohibited and reduced the study period and window for use. – Criterion 1c: reduced the study period and window for use of anti-MF therapy. Criterion 1e: clarified that investigational JAK inhibitors were prohibited within 4 weeks prior to randomization. Criterion 7: added thalassemia as a cause of clinically significant anemia.• Updated criteria for adjusting or stopping doses to provide guidance that investigator clinical discretion should be used and that in the event of grade 3 or 4 toxicity, relevant laboratory tests should be closely monitored per investigator clinical discretion.

18 December 2020	<p>Protocol Amendment 2 (continued):</p> <ul style="list-style-type: none"> • Clarified the anticipated risks of DAN to emphasize that the provided safety information references the approved indications for DAN and should be interpreted by the investigator for guidance when assessing participants in this study. • Updated criteria for crossing over to open-label MMB to add sponsor approval for short-term use of restricted anti-MF medication to treat severe splenic progression, revise criteria for splenic progression, and add sponsor approval for spleen volume measurements read locally. • Updated restricted treatment use for consistency with exclusion criterion 1 and to clearly define the beginning and end of the study period. • Added that alternative methods, including paper forms, could be used to record Patient Reported Outcome responses in exceptional circumstances, with sponsor approval. • Updated adverse event and serious adverse event reporting criteria and procedures. • Clarified requirements for hepatitis testing. • Added that local laboratory assessments could be used to determine eligibility, with sponsor approval, if central laboratory assessments were not available prior to day 1. • Clarified the window (+/- 7 days) for MFSAF assessments and PRO responses during the open-label extended treatment period. • Added that participants requiring antihypertensive medication should be closely monitored on the day of the first study drug dose and that medication could be administered if clinically necessary. • Added that investigators were to advise participants on the conservation of gametes prior to receiving study drug due to the possibility of infertility. • Updated DAN packaging configuration and procedures for receipt of study drug. • Added that a male condom must be used in combination with a diaphragm (with spermicide). • Added a protocol addendum for guidance on modified study procedures that could be followed during the Coronavirus 2019 (COVID-19) pandemic.
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported