Clinical trial results:
A Phase 3, Randomized Study to Evaluate the Efficacy of Momelotinib Versus Best Available Therapy in Anemic or Thrombocytopenic Subjects with Primary Myelofibrosis, Post-polycythemia Vera Myelofibrosis, or Post-essential Thrombocythemia Myelofibrosis who were Treated with Ruxolitinib

Summary

EudraCT number	2013-005007-13
Trial protocol	DE GB IT FR
Global end of trial date	25 April 2019

Results information

Result version number	v1 (current)
This version publication date	09 May 2021
First version publication date	09 May 2021

Trial information

Trial identification

Sponsor protocol code	GS-US-352-1214

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02101268
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Sierra Oncology, Inc.
Sponsor organisation address	46701 Commerce Center Drive, Plymouth, MI, United States, 48170
Public contact	Martha Bond, Sierra Oncology, Inc., +1 4165287431, mbond@sierraoncology.com
Scientific contact	Martha Bond, Sierra Oncology, Inc., +1 4165287431, mbond@sierraoncology.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	25 June 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	25 April 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the efficacy of momelotinib (MMB) versus best available therapy (BAT) in anemic or thrombocytopenic subjects with primary myelofibrosis (PMF), or post-polycythemia vera or post-essential thrombocythemia myelofibrosis (Post-PV/EF MF) who were treated with ruxolitinib as measured by splenic response rate at Week 24 (SRR24).

Protection of trial subjects:

The protocol, protocol amendments, consent forms, and study subject information sheets were submitted by each investigator to a duly constituted Independent Ethics Committee (IEC) or Institutional Review Board (IRB) for review and approval before study initiation. Protocol amendments and all revisions to the consent form or study subject information sheet after initial IEC/IRB approval were submitted by the investigator to the IEC/IRB for review and approval before implementation in accordance with regulatory requirements.

Study GS-US-352-1214 was conducted under a United States (US) Investigational New Drug (IND) application and in accordance with recognized international scientific and ethical standards, including but not limited to the International Council for Harmonisation (ICH) guideline for Good Clinical Practice (GCP) and the original principles embodied in the Declaration of Helsinki. These standards are consistent with the requirements of the US Code of Federal Regulations (CFR) Title 21, Part 312 (21CFR312), and the European Community Directive 2001/20/EC, as well as other local legislation.

Investigators (or designee[s]) were responsible for obtaining written informed consent from each individual who participated in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures. Subjects were informed that they were completely free to refuse to enter the study or to withdraw from it at any time for any reason.

Background therapy: -

Evidence for comparator:

The control for this study was Best available therapy. Allowable options for BAT included the investigator’s choice of any agent(s) approved for the treatment of MF or are standard of care in the region where the study was being conducted and for which data or guidelines supported the use of that agent in the management of patients with MF. These included but were not limited to chemotherapy (eg, hydroxyurea), anagrelide, a corticosteroid, hematopoietic growth factor, an immunomodulating agent, androgen, or interferon and may include no MF treatment, as well as more than 1 treatment. Best available therapy could have also included no active therapy, where clinically appropriate, beyond standard supportive care measures which were to be provided to subjects in both arms during the active treatment phase of the study. Multiple BAT agents could have been used in combination or sequentially. In contrast, use of other MF therapeutic agents including hematopoietic growth factor support was not allowed during the treatment phase for subjects in the MMB treatment arm.
Subjects randomized to BAT were allowed to receive ruxolitinib because of the absence of alternative approved or guideline-recommended therapies following ruxolitinib. This also reflects the lack of a universally-accepted definition of ruxolitinib treatment failure. In practice, ruxolitinib is often continued despite toxicity if side effects are considered manageable with dose reduction(s), or despite suboptimal disease control given the multifaceted nature of the illness where some disease manifestations may be assessed as potentially benefitting from the continuation of ruxolitinib therapy.

Actual start date of recruitment	19 June 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 16
Country: Number of subjects enrolled	United Kingdom: 10
Country: Number of subjects enrolled	France: 23
Country: Number of subjects enrolled	Germany: 16
Country: Number of subjects enrolled	Italy: 29
Country: Number of subjects enrolled	Canada: 10
Country: Number of subjects enrolled	United States: 33
Country: Number of subjects enrolled	Israel: 19
Worldwide total number of subjects	156
EEA total number of subjects	84

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)	55
From 65 to 84 years	101
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study was designed for subjects with PMF, post-PV MF, or post-ET MF whose prior treatment with ruxolitinib was associated with anemia and/or thrombocytopenia.

Pre-assignment

Screening details:

Subjects were required to be treated with ruxolitinib (RUX) for at least 28 days, complicated by hematologic toxicity characterized by a requirement for RBC transfusion while on RUX, OR, a dose adjustment of RUX to < 20 twice daily at start of or during RUX AND the occurrence of Grade 3 or 4 thrombocytopenia, anemia, or hematoma while on RUX.

Pre-assignment period milestones

Number of subjects started	244[1]
Number of subjects completed	156

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Physician decision: 1
Reason: Number of subjects	Consent withdrawn by subject: 3
Reason: Number of subjects	Adverse event, non-fatal: 2
Reason: Number of subjects	Outside of visit window: 10
Reason: Number of subjects	Other: 6
Reason: Number of subjects	Did not meet eligibility criteria: 66

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Of the 244 subjects that were screened for the study, 88 subjects were screen failed as described in the Subject Non-Completion reasons (primarily due to not meeting eligibility criteria). 156 subjects completed the baseline period and were randomized for the study.

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Momelotinib (MMB)

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Momelotinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects self-administered MMB tablets at 100 mg, 150 mg or 200 mg orally once daily.

Arm title	Best Available Therapy (BAT)

Arm description: -

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Momelotinib (MMB)	Best Available Therapy (BAT)
Started	104	52
Completed	104	52

Period 2

Period 2 title	Randomized Treatment Phase
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Momelotinib (MMB)

Arm description:

Momelotinib is a potent, orally-bioavailable small-molecule inhibitor of JAK1, JAK2 and uniquely amongst the development-stage JAK inhibitors, ACVR1. Subjects were randomized on a 2:1 basis to MMB:BAT. The starting dose of MMB for all subjects in the RT phase was 200 mg (or placebo equivalent) in a single tablet. Momelotinib was to be orally self-administered once daily in the morning, and thereafter at approximately the same time each day.

Arm type	Experimental
Investigational medicinal product name	Momelotinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects self-administered MMB tablets at 100 mg, 150 mg or 200 mg orally once daily.

Arm title	Best Available Therapy (BAT)

Arm description:

Subjects in the BAT treatment arm received treatment at doses and schedules determined by the investigator in accordance with standard of care. Therapy may have been changed at any time during the study except during the screening period. Regimens for BAT could include but were not limited to chemotherapy (eg, hydroxyurea), anagrelide, a corticosteroid, hematopoietic growth factor, an immunomodulating agent, androgen, or interferon and may include no MF treatment, as well as more than 1 treatment. Subjects were randomized 2:1 to MMB:BAT.

Arm type	Comparator

Investigational medicinal product name	Best Available Therapy
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The reference therapy in this study was BAT. Regimens for BAT could include but were not limited to chemotherapy (eg, hydroxyurea), anagrelide, a corticosteroid, hematopoietic growth factor, an immunomodulating agent, androgen, or interferon and may include no MF treatment, as well as more than 1 treatment.

Number of subjects in period 2	Momelotinib (MMB)	Best Available Therapy (BAT)
Started	104	52
Completed	77	41
Not completed	27	11
Physician decision	4	1
Consent withdrawn by subject	8	4
Symptomatic Spleen Growth	-	1
Adverse event, non-fatal	6	-
Death	5	4
Disease Progression	4	1

Period 3

Period 3 title	Extension Treatment Phase
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	MMB to MMB

Arm description:

Subjects randomized to the MMB group who tolerated and derived clinical benefit from MMB had the option to continue MMB treatment in an ET phase for up to an additional 204 weeks.

Arm type	Experimental
Investigational medicinal product name	Momelotinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects self-administered MMB tablets at 100 mg, 150 mg or 200 mg orally once daily.

Arm title	BAT to MMB

Arm description:

After completion of the RT phase, subjects randomized to the BAT treatment arm had the option to receive MMB 200 mg once daily in an ET phase for up to an additional 204 weeks.

Arm type	Experimental
Investigational medicinal product name	Momelotinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects self-administered MMB tablets at 100 mg, 150 mg or 200 mg orally once daily.

Number of subjects in period 3[2]	MMB to MMB	BAT to MMB
Started	64	40
Completed	0	0
Not completed	64	40
Physician decision	5	2
Consent withdrawn by subject	3	2
Adverse event, non-fatal	14	18
Death	5	1
Transferred to study SRA-MMB-4365	15	7
Disease Progression	13	6
Lack of efficacy	9	4

Notes:

[2] - 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: All subjects that participated in the Extension Treatment period either discontinued as described in the Subject Non-Completion Reasons or were transferred to the extended access study SRA-MMB-4365.

Baseline characteristics

Reporting groups	
Reporting group title	Momelotinib (MMB)
Reporting group description: -	
Reporting group title	Best Available Therapy (BAT)
Reporting group description: -	

Reporting group values	Momelotinib (MMB)	Best Available Therapy (BAT)	Total
Number of subjects	104	52	156
Age categorical Units: Subjects			
< 65 years	41	14	55
>= 65 years	63	38	101
Age continuous Units: years			
median	67.0	69.5	
full range (min-max)	61.5 to 72.0	64.0 to 75.0	-
Gender categorical Units: Subjects			
Female	69	24	93
Male	35	28	63
Race Units: Subjects			
White	83	44	127
Black or African American	6	0	6
Native Hawaiian or Other Pacific Islander	0	0	0
Asian	0	0	0
American Indian or Alaska Native	0	0	0
Not Permitted	15	8	23
Ethnicity Units: Subjects			
Hispanic or Latino	5	4	9
Not Hispanic or Latino	81	40	121
Not Permitted	18	8	26
Transfusion Dependent Units: Subjects			
Yes	58	27	85
No	46	25	71
Total Symptom Score (TSS) Units: Subjects			
< 18	61	28	89
>= 18	43	24	67
Weight Units: kg			
median	75.4	74.0	
inter-quartile range (Q1-Q3)	68.0 to 87.0	62.0 to 81.3	-
Height			

Units: cm			
median	170.0	168.0	
inter-quartile range (Q1-Q3)	164.0 to 177.8	160.0 to 175.0	-
Body Mass Index			
Units: kg/m^2			
median	25.9	26.1	
inter-quartile range (Q1-Q3)	23.6 to 28.2	23.5 to 29.1	-
Hemoglobin			
Units: g/dL			
median	9.0	9.2	
inter-quartile range (Q1-Q3)	7.9 to 10.7	8.5 to 10.1	-

Subject analysis sets

Subject analysis set title	Intent-to-Treat Analysis Set
Subject analysis set type	Intention-to-treat

Subject analysis set description:

For the RT phase, the ITT Analysis Set included all subjects who were randomized in the study. Subjects were grouped within the ITT by the treatment group to which they were randomized.
This is the primary analysis set for efficacy analyses and for demographic and baseline characteristics.
For the secondary efficacy endpoint of TSS response rate at Week 24, the analysis was performed on subjects in the ITT Analysis Set who had a baseline TSS > 0 or who had a baseline TSS = 0 but a nonzero or missing TSS at Week 24.

Reporting group values	Intent-to-Treat Analysis Set		
Number of subjects	156		
Age categorical			
Units: Subjects			
< 65 years	55		
>= 65 years	101		
Age continuous			
Units: years			
median	68.0		
full range (min-max)	62.0 to 73.5		
Gender categorical			
Units: Subjects			
Female	93		
Male	63		
Race			
Units: Subjects			
White	127		
Black or African American	6		
Native Hawaiian or Other Pacific Islander	0		
Asian	0		
American Indian or Alaska Native	0		
Not Permitted	23		
Ethnicity			
Units: Subjects			
Hispanic or Latino	9		
Not Hispanic or Latino	121		
Not Permitted	26		

Transfusion Dependent Units: Subjects			
Yes	85		
No	71		
Total Symptom Score (TSS) Units: Subjects			
< 18	89		
>= 18	67		
Weight Units: kg			
median	75.0		
inter-quartile range (Q1-Q3)	66.0 to 85.7		
Height Units: cm			
median	170.0		
inter-quartile range (Q1-Q3)	162.5 to 176.0		
Body Mass Index Units: kg/m^2			
median	26.0		
inter-quartile range (Q1-Q3)	23.6 to 28.6		
Hemoglobin Units: g/dL			
median	9.0		
inter-quartile range (Q1-Q3)	8.1 to 10.6		

End points

End points reporting groups

Reporting group title	Momelotinib (MMB)
Reporting group description: -	
Reporting group title	Best Available Therapy (BAT)
Reporting group description: -	
Reporting group title	Momelotinib (MMB)

Reporting group description:

Momelotinib is a potent, orally-bioavailable small-molecule inhibitor of JAK1, JAK2 and uniquely amongst the development-stage JAK inhibitors, ACVR1. Subjects were randomized on a 2:1 basis to MMB:BAT. The starting dose of MMB for all subjects in the RT phase was 200 mg (or placebo equivalent) in a single tablet. Momelotinib was to be orally self-administered once daily in the morning, and thereafter at approximately the same time each day.

Reporting group title	Best Available Therapy (BAT)

Reporting group description:

Subjects in the BAT treatment arm received treatment at doses and schedules determined by the investigator in accordance with standard of care. Therapy may have been changed at any time during the study except during the screening period. Regimens for BAT could include but were not limited to chemotherapy (eg, hydroxyurea), anagrelide, a corticosteroid, hematopoietic growth factor, an immunomodulating agent, androgen, or interferon and may include no MF treatment, as well as more than 1 treatment. Subjects were randomized 2:1 to MMB:BAT.

Reporting group title	MMB to MMB

Reporting group description:

Subjects randomized to the MMB group who tolerated and derived clinical benefit from MMB had the option to continue MMB treatment in an ET phase for up to an additional 204 weeks.

Reporting group title	BAT to MMB

Reporting group description:

After completion of the RT phase, subjects randomized to the BAT treatment arm had the option to receive MMB 200 mg once daily in an ET phase for up to an additional 204 weeks.

Subject analysis set title	Intent-to-Treat Analysis Set
Subject analysis set type	Intention-to-treat

Subject analysis set description:

For the RT phase, the ITT Analysis Set included all subjects who were randomized in the study. Subjects were grouped within the ITT by the treatment group to which they were randomized.
This is the primary analysis set for efficacy analyses and for demographic and baseline characteristics. For the secondary efficacy endpoint of TSS response rate at Week 24, the analysis was performed on subjects in the ITT Analysis Set who had a baseline TSS > 0 or who had a baseline TSS = 0 but a nonzero or missing TSS at Week 24.

Primary: Splenic Response Rate at Week 24

End point title	Splenic Response Rate at Week 24

End point description:

The primary endpoint of the study, splenic response rate at Week 24, was defined as the proportion of subjects who achieved a spleen volume reduction of ≥ 35% from baseline at the Week 24 assessment as measured by MRI or CT scans. A similar proportion of subjects achieved a response in the MMB group (6.7%, 7 of 104 subjects) as in the BAT group (5.8%, 3 of 52 subjects) in the ITT population. The difference in response rates was not statistically significant (proportion difference by stratified CMH method [95% CI]: 0.01 [−0.09, 0.10]; p = 0.90). Of the 3 responders in the BAT group, 1 subject received 5 mg ruxolitinib twice daily, increased to 10 mg twice daily, and prednisone/prednisolone; 1 subject received 5 mg ruxolitinib twice daily, prednisone/prednisolone, and hydroxyurea; and 1 subject received 20 mg ruxolitinib twice daily.

End point type	Primary

End point timeframe:

Week 24

End point values	Momelotinib (MMB)	Best Available Therapy (BAT)	Intent-to-Treat Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	104	52	156	
Units: Subjects				
Responder	7	3	10	
Non Responder	97	49	146	

Attachments (see zip file)	t-srr24.pdf

Statistical analyses

Statistical analysis title	Analysis of Splenic Response Rate

Statistical analysis description:

The primary endpoint was splenic response rate at Week 24 is defined as the proportion of subjects who achieved a ≥ 35% reduction in spleen volume at Week 24 versus baseline measured by MRI or CT.

Comparison groups	Momelotinib (MMB) v Best Available Therapy (BAT)
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9
Method	Cochran-Mantel-Haenszel
Parameter estimate	Proportion Difference - Stratified CMH
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.09
upper limit	0.1

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

End point title	Total Symptom Score (TSS) Response Rate at Week 24

End point description:

Response rate in TSS from baseline at Week 24, a prespecified secondary endpoint, was defined as the proportion of subjects who achieved a ≥ 50% reduction in TSS from baseline at Week 24 as measured by the modified MPN-SAF TSS v2.0 diary. Response rate in TSS at Week 24 was analyzed for subjects in the ITT who had a baseline TSS > 0 or subjects who had a baseline TSS = 0 but nonzero or missing TSS at Week 24. In the MMB group, 27 (26.2%) of the 103 evaluable patients had a TSS reduction of ≥ 50% from baseline compared to 3 (5.9%) of the 51 evaluable subjects in the BAT group, indicating a 4- to 5 fold greater symptomatic response improvement in subjects who received MMB compared to BAT. The proportion difference by stratified CMH method (95% CI) was 0.20 (0.09, 0.32); this difference was nominally significant ($p < 0.001$).

End point type	Secondary

End point timeframe:

Week 24

End point values	Momelotinib (MMB)	Best Available Therapy (BAT)	Intent-to-Treat Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	103	51	154	
Units: Subject				
Responder	27	3	30	
Non Responder	76	48	124	

Attachments (see zip file)	t-tss24.pdf

Statistical analyses

Statistical analysis title	Analysis of Response Rate in TSS at Week 24

Statistical analysis description:

Response rate in TSS from baseline to Week 24 is defined as the proportion of subjects who achieved a ≥ 50% reduction from baseline in TSS at Week 24 as measured by the modified MPN SAF TSS v2.0 diary

Comparison groups	Momelotinib (MMB) v Best Available Therapy (BAT)
Number of subjects included in analysis	154
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Proportion Difference - Stratified CMH
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.09
upper limit	0.32

Secondary: Rate of Red Blood Cell Transfusions in the RT

End point title	Rate of Red Blood Cell Transfusions in the RT

End point description:

The rate of RBC transfusions in the RT phase was a prespecified secondary endpoint, defined as the average number of RBC units not associated with clinically overt bleeding per subject-month during the RT Phase. For the ITT analysis set, the median (Q1, Q3) rate of RBC transfusion was lower in the MMB group (0.5 [0.0, 2.4] units/month) compared with the BAT group (1.2 [0.0, 2.8] units/month) through Week 24. The median (Q1, Q3) total number of RBC transfusion units through Week 24 was lower in the MMB group (2.0 [0.0, 11.0]) compared with the BAT group (6.0 [0.0, 10.5]).

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	Momelotinib (MMB)	Best Available Therapy (BAT)	Intent-to-Treat Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	104	52	156	
Units: units/month				
median (inter-quartile range (Q1-Q3))				
Responder	0.5 (0.0 to 2.4)	1.2 (0.0 to 2.8)	0.8 (0.0 to 2.6)	

Attachments (see zip file)	t-rbc24.pdf

Statistical analyses

Statistical analysis title	Analysis of Rate of RBC Transfusion in the RT

Statistical analysis description:

Rate of RBC transfusion in the RT phase is defined as the average number of RBC units transfused that was not associated with clinically overt bleeding per subject month during the RT phase

Comparison groups	Momelotinib (MMB) v Best Available Therapy (BAT)
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.38
Method	Negative Binomial Model, Adjusted
Parameter estimate	Rate ratio of RBC transfusion
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	1.31

Secondary: RBC Transfusion Independence Rate at Week 24

End point title	RBC Transfusion Independence Rate at Week 24

End point description:

Red blood cell TI at Week 24 is defined as the absence of RBC transfusion and no hemoglobin level < 8 g/dL in the prior 12 weeks, excluding cases associated with clinically overt bleeding. A nominally greater proportion of subjects in the MMB group was TI at Week 24 (43.3%, 45 subjects) compared with the BAT group (21.2%, 11 subjects) despite containing a lower proportion of TI subjects in the MMB group at baseline (MMB: 30.8%; BAT: 36.5%). The difference was nominally significant (p = 0.001). Overall, the proportion of subjects with TI status increased by 12.5% in the MMB group and decreased by 15.3% in the BAT group at Week 24 compared to baseline.

End point type	Secondary

End point timeframe:

Week 24

End point values	Momelotinib (MMB)	Best Available Therapy (BAT)	Intent-to-Treat Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	104	52	156	
Units: Subjects				
Responder	45	11	56	
Non-Responder	59	41	100	

Attachments (see zip file)	t-rbcti24.pdf

Statistical analyses

Statistical analysis title	Analysis of RBC TI Rate at Week 24

Statistical analysis description:

Response rate for TI at Week 24 is defined as the proportion of subjects who were TI at Week 24, where TI was defined as absence of RBC transfusion and no hemoglobin level below 8 g/dL in the prior 12 weeks, excluding cases associated with clinically overt bleeding.

Comparison groups	Momelotinib (MMB) v Best Available Therapy (BAT)
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Proportion Difference - Stratified CMH
Point estimate	0.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.09
upper limit	0.37

Secondary: RBC Transfusion Dependence Rate at Week 24

End point title	RBC Transfusion Dependence Rate at Week 24

End point description:

Red blood cell TD rate at Week 24 for the ITT population was a prespecified secondary endpoint, and was defined as having had at least 4 units of RBC transfusion or a hemoglobin level below 8 g/dL in the prior 8 weeks ending with Week 24 (excluding cases associated with clinically overt bleeding). Subjects with the last RT phase participation date prior to Day 162 (ie. missing at Week 24) were considered TD at Week 24. A smaller proportion of the MMB group was TD at Week 24 (50.0%, 52 subjects) compared with the BAT group (63.5%, 33 subjects). The difference was not statistically significant.

End point type	Secondary

End point timeframe:

Week 24

End point values	Momelotinib (MMB)	Best Available Therapy (BAT)	Intent-to-Treat Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	104	52	71	
Units: Subjects				
Dependent	52	33	85	
Not-Dependent	52	19	71	

Attachments (see zip file)	t-rbctd24.pdf

Statistical analyses

Statistical analysis title	Analysis of RBC TD Rate at Week 24

Statistical analysis description:

Response rate for TD at Week 24 is defined as the proportion of subjects who were transfusion dependent at Week 24, where TD was defined as at least 4 units of RBC transfusion or a hemoglobin level below 8 g/dL in the prior 8 weeks excluding cases associated with clinically overt bleeding

Comparison groups	Momelotinib (MMB) v Best Available Therapy (BAT)
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1
Method	Cochran-Mantel-Haenszel
Parameter estimate	Proportion Difference - Stratified CMH
Point estimate	-0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.29
upper limit	0.03

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were recorded that occurred from initiation of investigational product (IP) until 30 days after the last administration of IP regardless of cause or relationship.

Adverse event reporting additional description:

All adverse events were recorded in the eCRF database. Serious adverse events needed to be reported within 24 hours of investigator being aware. Severity of AEs were graded using the CTCAE, Version 4.03, per AE (episode) the highest severity grade attained should be reported. All AEs were followed up until resolution when possible.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Momelotinib (MMB)
Reporting group description: -	
Reporting group title	Best Available Therapy (BAT)
Reporting group description: -	
Reporting group title	MMB to MMB
Reporting group description: -	
Reporting group title	BAT to MMB

Reporting group description: -

Serious adverse events	Momelotinib (MMB)	Best Available Therapy (BAT)	MMB to MMB
Total subjects affected by serious adverse events			
subjects affected / exposed	37 / 104 (35.58%)	12 / 52 (23.08%)	33 / 64 (51.56%)
number of deaths (all causes)	8	5	29
number of deaths resulting from adverse events	6	4	14
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant melanoma			
subjects affected / exposed	1 / 104 (0.96%)	0 / 52 (0.00%)	0 / 64 (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
Lung adenocarcinoma			
subjects affected / exposed	0 / 104 (0.00%)	1 / 52 (1.92%)	0 / 64 (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
Metastatic squamous cell carcinoma			

subjects affected / exposed	0 / 104 (0.00%)	0 / 52 (0.00%)	0 / 64 (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
Papillary thyroid cancer			
subjects affected / exposed	0 / 104 (0.00%)	0 / 52 (0.00%)	0 / 64 (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
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	1 / 104 (0.96%)	0 / 52 (0.00%)	0 / 64 (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
Diabetic vascular disorder			
subjects affected / exposed	0 / 104 (0.00%)	1 / 52 (1.92%)	0 / 64 (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
Embolism			
subjects affected / exposed	0 / 104 (0.00%)	0 / 52 (0.00%)	2 / 64 (3.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis			
subjects affected / exposed	0 / 104 (0.00%)	0 / 52 (0.00%)	1 / 64 (1.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	2 / 104 (1.92%)	2 / 52 (3.85%)	0 / 64 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	2 / 104 (1.92%)	0 / 52 (0.00%)	2 / 64 (3.13%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Generalised oedema			
subjects affected / exposed	1 / 104 (0.96%)	0 / 52 (0.00%)	0 / 64 (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
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 104 (0.96%)	0 / 52 (0.00%)	0 / 64 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Postmenopausal haemorrhage			
subjects affected / exposed	1 / 104 (0.96%)	0 / 52 (0.00%)	0 / 64 (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
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	2 / 104 (1.92%)	0 / 52 (0.00%)	1 / 64 (1.56%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	1 / 2	0 / 0	0 / 0
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 104 (0.96%)	0 / 52 (0.00%)	0 / 64 (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
Dyspnoea			
subjects affected / exposed	1 / 104 (0.96%)	0 / 52 (0.00%)	0 / 64 (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
Pleural effusion			
subjects affected / exposed	1 / 104 (0.96%)	0 / 52 (0.00%)	0 / 64 (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
Pulmonary congestion			

subjects affected / exposed	0 / 104 (0.00%)	1 / 52 (1.92%)	0 / 64 (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
Pulmonary hypertension			
subjects affected / exposed	0 / 104 (0.00%)	0 / 52 (0.00%)	0 / 64 (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
Respiratory distress			
subjects affected / exposed	0 / 104 (0.00%)	0 / 52 (0.00%)	1 / 64 (1.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pneumonia aspiration			
subjects affected / exposed	0 / 104 (0.00%)	0 / 52 (0.00%)	2 / 64 (3.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pneumonitis			
subjects affected / exposed	0 / 104 (0.00%)	0 / 52 (0.00%)	2 / 64 (3.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung disorder			
subjects affected / exposed	0 / 104 (0.00%)	0 / 52 (0.00%)	1 / 64 (1.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 104 (0.00%)	0 / 52 (0.00%)	0 / 64 (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
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 104 (0.00%)	0 / 52 (0.00%)	0 / 64 (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
Investigations			

Blood creatinine increased			
subjects affected / exposed	1 / 104 (0.96%)	0 / 52 (0.00%)	0 / 64 (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	1 / 104 (0.96%)	0 / 52 (0.00%)	0 / 64 (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
Subdural haematoma			
subjects affected / exposed	1 / 104 (0.96%)	0 / 52 (0.00%)	0 / 64 (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
Post lumbar puncture syndrome			
subjects affected / exposed	0 / 104 (0.00%)	0 / 52 (0.00%)	1 / 64 (1.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	0 / 104 (0.00%)	0 / 52 (0.00%)	2 / 64 (3.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint dislocation			
subjects affected / exposed	0 / 104 (0.00%)	0 / 52 (0.00%)	1 / 64 (1.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Procedural pain			
subjects affected / exposed	0 / 104 (0.00%)	0 / 52 (0.00%)	1 / 64 (1.56%)
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			
Cardiac failure			
subjects affected / exposed	3 / 104 (2.88%)	1 / 52 (1.92%)	1 / 64 (1.56%)
occurrences causally related to treatment / all	1 / 3	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1

Supraventricular tachycardia			
subjects affected / exposed	2 / 104 (1.92%)	0 / 52 (0.00%)	0 / 64 (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
Angina unstable			
subjects affected / exposed	1 / 104 (0.96%)	0 / 52 (0.00%)	0 / 64 (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
Atrial fibrillation			
subjects affected / exposed	1 / 104 (0.96%)	0 / 52 (0.00%)	1 / 64 (1.56%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	1 / 104 (0.96%)	0 / 52 (0.00%)	0 / 64 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	1 / 104 (0.96%)	0 / 52 (0.00%)	1 / 64 (1.56%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Left ventricular failure			
subjects affected / exposed	0 / 104 (0.00%)	0 / 52 (0.00%)	1 / 64 (1.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 104 (0.00%)	0 / 52 (0.00%)	0 / 64 (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
Myocardial ischaemia			
subjects affected / exposed	0 / 104 (0.00%)	0 / 52 (0.00%)	0 / 64 (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
Tachycardia			

subjects affected / exposed	0 / 104 (0.00%)	1 / 52 (1.92%)	1 / 64 (1.56%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction			
subjects affected / exposed	0 / 104 (0.00%)	0 / 52 (0.00%)	1 / 64 (1.56%)
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 acute			
subjects affected / exposed	0 / 104 (0.00%)	0 / 52 (0.00%)	1 / 64 (1.56%)
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			
Presyncope			
subjects affected / exposed	2 / 104 (1.92%)	0 / 52 (0.00%)	0 / 64 (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
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 104 (0.96%)	0 / 52 (0.00%)	0 / 64 (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
Restless legs syndrome			
subjects affected / exposed	1 / 104 (0.96%)	0 / 52 (0.00%)	0 / 64 (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
Dizziness			
subjects affected / exposed	0 / 104 (0.00%)	0 / 52 (0.00%)	1 / 64 (1.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 14
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 104 (0.00%)	0 / 52 (0.00%)	2 / 64 (3.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cerebrovascular accident			

subjects affected / exposed	0 / 104 (0.00%)	0 / 52 (0.00%)	1 / 64 (1.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 104 (0.00%)	0 / 52 (0.00%)	1 / 64 (1.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 104 (3.85%)	0 / 52 (0.00%)	1 / 64 (1.56%)
occurrences causally related to treatment / all	2 / 9	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spontaneous haematoma			
subjects affected / exposed	1 / 104 (0.96%)	0 / 52 (0.00%)	0 / 64 (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
Lymphadenopathy			
subjects affected / exposed	0 / 104 (0.00%)	1 / 52 (1.92%)	0 / 64 (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
Splenic infarction			
subjects affected / exposed	0 / 104 (0.00%)	0 / 52 (0.00%)	0 / 64 (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
Haematoma			
subjects affected / exposed	0 / 104 (0.00%)	1 / 52 (1.92%)	1 / 64 (1.56%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vestibular disorder			
subjects affected / exposed	0 / 104 (0.00%)	1 / 52 (1.92%)	0 / 64 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			

Retinal vein thrombosis			
subjects affected / exposed	0 / 104 (0.00%)	0 / 52 (0.00%)	1 / 64 (1.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastrointestinal haemorrhage			
subjects affected / exposed	2 / 104 (1.92%)	0 / 52 (0.00%)	2 / 64 (3.13%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	2 / 104 (1.92%)	0 / 52 (0.00%)	0 / 64 (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
Abdominal pain upper			
subjects affected / exposed	1 / 104 (0.96%)	0 / 52 (0.00%)	0 / 64 (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
Ascites			
subjects affected / exposed	1 / 104 (0.96%)	1 / 52 (1.92%)	1 / 64 (1.56%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	1 / 104 (0.96%)	0 / 52 (0.00%)	0 / 64 (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
Gastric ulcer			
subjects affected / exposed	1 / 104 (0.96%)	0 / 52 (0.00%)	0 / 64 (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 angiodysplasia			
subjects affected / exposed	1 / 104 (0.96%)	0 / 52 (0.00%)	0 / 64 (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
Haematemesis			

subjects affected / exposed	1 / 104 (0.96%)	0 / 52 (0.00%)	1 / 64 (1.56%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	0 / 104 (0.00%)	2 / 52 (3.85%)	0 / 64 (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
Large intestinal haemorrhage			
subjects affected / exposed	0 / 104 (0.00%)	0 / 52 (0.00%)	0 / 64 (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
Varices oesophageal			
subjects affected / exposed	0 / 104 (0.00%)	1 / 52 (1.92%)	0 / 64 (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
Abdominal wall haematoma			
subjects affected / exposed	0 / 104 (0.00%)	0 / 52 (0.00%)	0 / 64 (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
Melaena			
subjects affected / exposed	0 / 104 (0.00%)	0 / 52 (0.00%)	1 / 64 (1.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	0 / 104 (0.00%)	0 / 52 (0.00%)	0 / 64 (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
Visceral venous thrombosis			
subjects affected / exposed	0 / 104 (0.00%)	0 / 52 (0.00%)	0 / 64 (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
Hepatobiliary disorders			
Hepatic cirrhosis			

subjects affected / exposed	0 / 104 (0.00%)	1 / 52 (1.92%)	0 / 64 (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
Hepatic failure			
subjects affected / exposed	0 / 104 (0.00%)	0 / 52 (0.00%)	1 / 64 (1.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Skin and subcutaneous tissue disorders			
Erythema multiforme			
subjects affected / exposed	0 / 104 (0.00%)	0 / 52 (0.00%)	0 / 64 (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
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 104 (1.92%)	0 / 52 (0.00%)	2 / 64 (3.13%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	1 / 104 (0.96%)	0 / 52 (0.00%)	0 / 64 (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
Renal failure			
subjects affected / exposed	1 / 104 (0.96%)	0 / 52 (0.00%)	2 / 64 (3.13%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Ureterolithiasis			
subjects affected / exposed	0 / 104 (0.00%)	0 / 52 (0.00%)	1 / 64 (1.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			
subjects affected / exposed	0 / 104 (0.00%)	0 / 52 (0.00%)	1 / 64 (1.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephritis			

subjects affected / exposed	0 / 104 (0.00%)	0 / 52 (0.00%)	1 / 64 (1.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Renal impairment			
subjects affected / exposed	0 / 104 (0.00%)	0 / 52 (0.00%)	1 / 64 (1.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 104 (0.96%)	0 / 52 (0.00%)	0 / 64 (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
Groin pain			
subjects affected / exposed	1 / 104 (0.96%)	0 / 52 (0.00%)	0 / 64 (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
Muscular weakness			
subjects affected / exposed	0 / 104 (0.00%)	0 / 52 (0.00%)	0 / 64 (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
Chondrocalcinosis pyrophosphate			
subjects affected / exposed	0 / 104 (0.00%)	0 / 52 (0.00%)	0 / 64 (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
Joint effusion			
subjects affected / exposed	0 / 104 (0.00%)	0 / 52 (0.00%)	0 / 64 (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
Osteoarthritis			
subjects affected / exposed	0 / 104 (0.00%)	0 / 52 (0.00%)	0 / 64 (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
Infections and infestations			

Cellulitis			
subjects affected / exposed	2 / 104 (1.92%)	0 / 52 (0.00%)	1 / 64 (1.56%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	2 / 104 (1.92%)	1 / 52 (1.92%)	6 / 64 (9.38%)
occurrences causally related to treatment / all	1 / 2	0 / 1	3 / 9
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Sepsis			
subjects affected / exposed	2 / 104 (1.92%)	2 / 52 (3.85%)	4 / 64 (6.25%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 1
Bacterial sepsis			
subjects affected / exposed	1 / 104 (0.96%)	0 / 52 (0.00%)	0 / 64 (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
Diverticulitis			
subjects affected / exposed	1 / 104 (0.96%)	0 / 52 (0.00%)	0 / 64 (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
Enterobacter bacteraemia			
subjects affected / exposed	1 / 104 (0.96%)	0 / 52 (0.00%)	0 / 64 (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
Lung Infection			
subjects affected / exposed	1 / 104 (0.96%)	0 / 52 (0.00%)	1 / 64 (1.56%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ophthalmic herpes zoster			
subjects affected / exposed	1 / 104 (0.96%)	0 / 52 (0.00%)	0 / 64 (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
Peritonitis bacterial			

subjects affected / exposed	1 / 104 (0.96%)	0 / 52 (0.00%)	0 / 64 (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
Sinusitis			
subjects affected / exposed	1 / 104 (0.96%)	0 / 52 (0.00%)	0 / 64 (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 respiratory tract infection			
subjects affected / exposed	1 / 104 (0.96%)	0 / 52 (0.00%)	1 / 64 (1.56%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile infection			
subjects affected / exposed	0 / 104 (0.00%)	0 / 52 (0.00%)	1 / 64 (1.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related sepsis			
subjects affected / exposed	0 / 104 (0.00%)	1 / 52 (1.92%)	0 / 64 (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
Gastroenteritis			
subjects affected / exposed	0 / 104 (0.00%)	1 / 52 (1.92%)	0 / 64 (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
Herpes zoster			
subjects affected / exposed	0 / 104 (0.00%)	1 / 52 (1.92%)	0 / 64 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	0 / 104 (0.00%)	1 / 52 (1.92%)	0 / 64 (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
Urosepsis			

subjects affected / exposed	0 / 104 (0.00%)	0 / 52 (0.00%)	0 / 64 (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
Bronchitis			
subjects affected / exposed	0 / 104 (0.00%)	0 / 52 (0.00%)	1 / 64 (1.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacteraemia			
subjects affected / exposed	0 / 104 (0.00%)	0 / 52 (0.00%)	1 / 64 (1.56%)
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 bacteraemia			
subjects affected / exposed	0 / 104 (0.00%)	0 / 52 (0.00%)	0 / 64 (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
Infection			
subjects affected / exposed	0 / 104 (0.00%)	0 / 52 (0.00%)	1 / 64 (1.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 104 (0.00%)	0 / 52 (0.00%)	0 / 64 (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
Otitis media			
subjects affected / exposed	0 / 104 (0.00%)	0 / 52 (0.00%)	1 / 64 (1.56%)
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 viral			
subjects affected / exposed	0 / 104 (0.00%)	0 / 52 (0.00%)	1 / 64 (1.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Soft tissue infection			

subjects affected / exposed	0 / 104 (0.00%)	0 / 52 (0.00%)	0 / 64 (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
Urinary tract infection			
subjects affected / exposed	0 / 104 (0.00%)	0 / 52 (0.00%)	1 / 64 (1.56%)
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			
Tumour lysis syndrome			
subjects affected / exposed	1 / 104 (0.96%)	0 / 52 (0.00%)	0 / 64 (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
Decreased appetite			
subjects affected / exposed	0 / 104 (0.00%)	1 / 52 (1.92%)	0 / 64 (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
Diabetes mellitus			
subjects affected / exposed	0 / 104 (0.00%)	0 / 52 (0.00%)	2 / 64 (3.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 104 (0.00%)	0 / 52 (0.00%)	0 / 64 (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
Gout			
subjects affected / exposed	0 / 104 (0.00%)	0 / 52 (0.00%)	1 / 64 (1.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	BAT to MMB		
Total subjects affected by serious adverse events			
subjects affected / exposed	19 / 40 (47.50%)		
number of deaths (all causes)	18		
number of deaths resulting from adverse events	3		

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant melanoma			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lung adenocarcinoma			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metastatic squamous cell carcinoma			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Papillary thyroid cancer			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diabetic vascular disorder			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Embolism			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Deep vein thrombosis			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Generalised oedema			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Postmenopausal haemorrhage			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			

subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary congestion				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary hypertension				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory distress				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia aspiration				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonitis				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lung disorder				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				

subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Confusional state				
subjects affected / exposed	2 / 40 (5.00%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Investigations				
Blood creatinine increased				
subjects affected / exposed	0 / 40 (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	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Subdural haematoma				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Post lumbar puncture syndrome				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Fall				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Joint dislocation				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Procedural pain				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Cardiac failure				
subjects affected / exposed	2 / 40 (5.00%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Supraventricular tachycardia				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Angina unstable				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Atrial fibrillation				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac arrest				
subjects affected / exposed	0 / 40 (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 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Left ventricular failure				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Myocardial infarction				

subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Myocardial ischaemia				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tachycardia				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Acute myocardial infarction				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac failure acute				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Presyncope				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Peripheral sensory neuropathy				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Restless legs syndrome				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dizziness				

subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Subarachnoid haemorrhage				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cerebrovascular accident				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	0 / 40 (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	4 / 40 (10.00%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	0 / 0			
Spontaneous haematoma				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lymphadenopathy				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Splenic infarction				
subjects affected / exposed	3 / 40 (7.50%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Haematoma				

subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Vestibular disorder			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Retinal vein thrombosis			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 40 (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 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Abdominal pain upper			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ascites			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Gastric ulcer				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal angiodysplasia				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haematemesis				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Abdominal pain				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Large intestinal haemorrhage				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Varices oesophageal				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Abdominal wall haematoma				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Melaena				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rectal haemorrhage				

subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Visceral venous thrombosis			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hepatic cirrhosis			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatic failure			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Erythema multiforme			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nephrolithiasis			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal failure			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Ureterolithiasis				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haematuria				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nephritis				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal impairment				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Back pain				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Groin pain				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Muscular weakness				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Chondrocalcinosis pyrophosphate				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Joint effusion				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Osteoarthritis				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Cellulitis				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Sepsis				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Bacterial sepsis				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diverticulitis				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Enterobacter bacteraemia				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lung Infection				

subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Ophthalmic herpes zoster				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Peritonitis bacterial				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sinusitis				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Upper respiratory tract infection				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Clostridium difficile infection				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Device related sepsis				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Herpes zoster				

subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lower respiratory tract infection				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urosepsis				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Bronchitis				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Bacteraemia				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Escherichia bacteraemia				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infection				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Influenza				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Otitis media				

subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia viral				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Soft tissue infection				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Tumour lysis syndrome				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Decreased appetite				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diabetes mellitus				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hyponatraemia				
subjects affected / exposed	2 / 40 (5.00%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Gout				

subjects affected / exposed	0 / 40 (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	Momelotinib (MMB)	Best Available Therapy (BAT)	MMB to MMB
Total subjects affected by non-serious adverse events			
subjects affected / exposed	99 / 104 (95.19%)	46 / 52 (88.46%)	63 / 64 (98.44%)
Vascular disorders			
hypertension			
subjects affected / exposed	10 / 104 (9.62%)	2 / 52 (3.85%)	5 / 64 (7.81%)
occurrences (all)	29	3	9
Hypotension			
subjects affected / exposed	3 / 104 (2.88%)	2 / 52 (3.85%)	2 / 64 (3.13%)
occurrences (all)	6	2	2
Haematoma			
subjects affected / exposed	0 / 104 (0.00%)	0 / 52 (0.00%)	2 / 64 (3.13%)
occurrences (all)	0	0	2
General disorders and administration site conditions			
Ascites			
subjects affected / exposed	4 / 104 (3.85%)	2 / 52 (3.85%)	2 / 64 (3.13%)
occurrences (all)	5	2	4
Asthenia			
subjects affected / exposed	20 / 104 (19.23%)	11 / 52 (21.15%)	8 / 64 (12.50%)
occurrences (all)	33	19	13
Fatigue			
subjects affected / exposed	16 / 104 (15.38%)	10 / 52 (19.23%)	7 / 64 (10.94%)
occurrences (all)	18	14	7
Pyrexia			
subjects affected / exposed	13 / 104 (12.50%)	4 / 52 (7.69%)	16 / 64 (25.00%)
occurrences (all)	20	5	22
Oedema peripheral			
subjects affected / exposed	11 / 104 (10.58%)	6 / 52 (11.54%)	10 / 64 (15.63%)
occurrences (all)	15	6	13

Early satiety			
subjects affected / exposed	3 / 104 (2.88%)	6 / 52 (11.54%)	2 / 64 (3.13%)
occurrences (all)	4	6	2
Chills			
subjects affected / exposed	2 / 104 (1.92%)	0 / 52 (0.00%)	2 / 64 (3.13%)
occurrences (all)	3	0	2
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	18 / 104 (17.31%)	6 / 52 (11.54%)	17 / 64 (26.56%)
occurrences (all)	22	7	27
Dyspnoea			
subjects affected / exposed	12 / 104 (11.54%)	7 / 52 (13.46%)	5 / 64 (7.81%)
occurrences (all)	18	7	5
Epistaxis			
subjects affected / exposed	8 / 104 (7.69%)	6 / 52 (11.54%)	2 / 64 (3.13%)
occurrences (all)	9	9	2
Pneumonitis			
subjects affected / exposed	0 / 104 (0.00%)	0 / 52 (0.00%)	1 / 64 (1.56%)
occurrences (all)	0	0	1
Pulmonary oedema			
subjects affected / exposed	0 / 104 (0.00%)	0 / 52 (0.00%)	0 / 64 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	3 / 104 (2.88%)	4 / 52 (7.69%)	4 / 64 (6.25%)
occurrences (all)	3	4	4
Investigations			
Weight decreased			
subjects affected / exposed	10 / 104 (9.62%)	3 / 52 (5.77%)	7 / 64 (10.94%)
occurrences (all)	10	3	7
Blood creatinine increased			
subjects affected / exposed	6 / 104 (5.77%)	0 / 52 (0.00%)	5 / 64 (7.81%)
occurrences (all)	7	0	5
Injury, poisoning and procedural complications			
Contusion			

subjects affected / exposed	5 / 104 (4.81%)	3 / 52 (5.77%)	2 / 64 (3.13%)
occurrences (all)	6	3	2
Fall			
subjects affected / exposed	2 / 104 (1.92%)	2 / 52 (3.85%)	3 / 64 (4.69%)
occurrences (all)	2	2	3
Procedural pain			
subjects affected / exposed	0 / 104 (0.00%)	1 / 52 (1.92%)	0 / 64 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	1 / 104 (0.96%)	1 / 52 (1.92%)	1 / 64 (1.56%)
occurrences (all)	1	1	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	16 / 104 (15.38%)	4 / 52 (7.69%)	6 / 64 (9.38%)
occurrences (all)	19	4	6
Headache			
subjects affected / exposed	16 / 104 (15.38%)	3 / 52 (5.77%)	4 / 64 (6.25%)
occurrences (all)	20	4	5
Paraesthesia			
subjects affected / exposed	8 / 104 (7.69%)	1 / 52 (1.92%)	4 / 64 (6.25%)
occurrences (all)	11	1	4
Peripheral sensory neuropathy			
subjects affected / exposed	7 / 104 (6.73%)	0 / 52 (0.00%)	6 / 64 (9.38%)
occurrences (all)	9	0	8
Somnolence			
subjects affected / exposed	2 / 104 (1.92%)	1 / 52 (1.92%)	0 / 64 (0.00%)
occurrences (all)	2	1	0
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	18 / 104 (17.31%)	6 / 52 (11.54%)	8 / 64 (12.50%)
occurrences (all)	30	9	13
Anaemia			
subjects affected / exposed	15 / 104 (14.42%)	10 / 52 (19.23%)	14 / 64 (21.88%)
occurrences (all)	24	16	40
Neutropenia			

subjects affected / exposed	7 / 104 (6.73%)	1 / 52 (1.92%)	2 / 64 (3.13%)
occurrences (all)	10	3	4
Splenomegaly			
subjects affected / exposed	2 / 104 (1.92%)	3 / 52 (5.77%)	1 / 64 (1.56%)
occurrences (all)	3	3	1
Leukocytosis			
subjects affected / exposed	1 / 104 (0.96%)	0 / 52 (0.00%)	5 / 64 (7.81%)
occurrences (all)	1	0	5
Eye disorders			
Dry eye			
subjects affected / exposed	0 / 104 (0.00%)	0 / 52 (0.00%)	0 / 64 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	33 / 104 (31.73%)	8 / 52 (15.38%)	19 / 64 (29.69%)
occurrences (all)	42	16	26
Nausea			
subjects affected / exposed	20 / 104 (19.23%)	5 / 52 (9.62%)	8 / 64 (12.50%)
occurrences (all)	25	6	10
Abdominal pain			
subjects affected / exposed	16 / 104 (15.38%)	7 / 52 (13.46%)	7 / 64 (10.94%)
occurrences (all)	22	9	14
Constipation			
subjects affected / exposed	11 / 104 (10.58%)	2 / 52 (3.85%)	5 / 64 (7.81%)
occurrences (all)	15	2	7
Dyspepsia			
subjects affected / exposed	10 / 104 (9.62%)	1 / 52 (1.92%)	2 / 64 (3.13%)
occurrences (all)	10	1	2
Abdominal pain upper			
subjects affected / exposed	8 / 104 (7.69%)	1 / 52 (1.92%)	2 / 64 (3.13%)
occurrences (all)	8	1	2
Vomiting			
subjects affected / exposed	7 / 104 (6.73%)	1 / 52 (1.92%)	5 / 64 (7.81%)
occurrences (all)	7	1	7
Abdominal distension			

subjects affected / exposed	1 / 104 (0.96%)	3 / 52 (5.77%)	3 / 64 (4.69%)
occurrences (all)	1	4	3
Dry mouth			
subjects affected / exposed	2 / 104 (1.92%)	1 / 52 (1.92%)	1 / 64 (1.56%)
occurrences (all)	2	1	1
Melaena			
subjects affected / exposed	1 / 104 (0.96%)	1 / 52 (1.92%)	2 / 64 (3.13%)
occurrences (all)	1	1	2
Dysphagia			
subjects affected / exposed	1 / 104 (0.96%)	0 / 52 (0.00%)	0 / 64 (0.00%)
occurrences (all)	1	0	0
Abdominal wall haematoma			
subjects affected / exposed	0 / 104 (0.00%)	0 / 52 (0.00%)	0 / 64 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	13 / 104 (12.50%)	4 / 52 (7.69%)	8 / 64 (12.50%)
occurrences (all)	19	4	9
Night sweats			
subjects affected / exposed	8 / 104 (7.69%)	4 / 52 (7.69%)	3 / 64 (4.69%)
occurrences (all)	10	4	5
Hyperhidrosis			
subjects affected / exposed	5 / 104 (4.81%)	5 / 52 (9.62%)	3 / 64 (4.69%)
occurrences (all)	5	7	4
Alopecia			
subjects affected / exposed	1 / 104 (0.96%)	0 / 52 (0.00%)	4 / 64 (6.25%)
occurrences (all)	1	0	4
Dry skin			
subjects affected / exposed	2 / 104 (1.92%)	0 / 52 (0.00%)	1 / 64 (1.56%)
occurrences (all)	2	0	1
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 104 (0.96%)	0 / 52 (0.00%)	3 / 64 (4.69%)
occurrences (all)	1	0	4
Dysuria			

subjects affected / exposed	1 / 104 (0.96%)	0 / 52 (0.00%)	2 / 64 (3.13%)
occurrences (all)	1	0	4
Renal failure			
subjects affected / exposed	0 / 104 (0.00%)	0 / 52 (0.00%)	2 / 64 (3.13%)
occurrences (all)	0	0	2
Urinary incontinence			
subjects affected / exposed	0 / 104 (0.00%)	0 / 52 (0.00%)	1 / 64 (1.56%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	10 / 104 (9.62%)	4 / 52 (7.69%)	6 / 64 (9.38%)
occurrences (all)	10	4	6
Back pain			
subjects affected / exposed	5 / 104 (4.81%)	4 / 52 (7.69%)	9 / 64 (14.06%)
occurrences (all)	7	4	9
Pain in extremity			
subjects affected / exposed	5 / 104 (4.81%)	5 / 52 (9.62%)	7 / 64 (10.94%)
occurrences (all)	5	5	7
Bone pain			
subjects affected / exposed	2 / 104 (1.92%)	6 / 52 (11.54%)	2 / 64 (3.13%)
occurrences (all)	2	6	2
Muscle spasms			
subjects affected / exposed	3 / 104 (2.88%)	1 / 52 (1.92%)	5 / 64 (7.81%)
occurrences (all)	3	1	9
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	11 / 104 (10.58%)	4 / 52 (7.69%)	8 / 64 (12.50%)
occurrences (all)	15	7	14
Upper respiratory tract infection			
subjects affected / exposed	9 / 104 (8.65%)	3 / 52 (5.77%)	8 / 64 (12.50%)
occurrences (all)	9	4	10
Oral herpes			
subjects affected / exposed	7 / 104 (6.73%)	0 / 52 (0.00%)	2 / 64 (3.13%)
occurrences (all)	7	0	2
Bronchitis			

subjects affected / exposed	5 / 104 (4.81%)	2 / 52 (3.85%)	6 / 64 (9.38%)
occurrences (all)	5	3	6
Nasopharyngitis			
subjects affected / exposed	4 / 104 (3.85%)	2 / 52 (3.85%)	3 / 64 (4.69%)
occurrences (all)	4	3	3
Pneumonia			
subjects affected / exposed	1 / 104 (0.96%)	0 / 52 (0.00%)	4 / 64 (6.25%)
occurrences (all)	1	0	4
Oral candidiasis			
subjects affected / exposed	2 / 104 (1.92%)	1 / 52 (1.92%)	0 / 64 (0.00%)
occurrences (all)	2	1	0
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	8 / 104 (7.69%)	1 / 52 (1.92%)	5 / 64 (7.81%)
occurrences (all)	8	1	6
Decreased appetite			
subjects affected / exposed	7 / 104 (6.73%)	2 / 52 (3.85%)	4 / 64 (6.25%)
occurrences (all)	8	2	5
Vitamin B1 deficiency			
subjects affected / exposed	7 / 104 (6.73%)	2 / 52 (3.85%)	6 / 64 (9.38%)
occurrences (all)	7	2	6
Hyperuricaemia			
subjects affected / exposed	6 / 104 (5.77%)	2 / 52 (3.85%)	4 / 64 (6.25%)
occurrences (all)	7	2	5
Hypokalaemia			
subjects affected / exposed	4 / 104 (3.85%)	0 / 52 (0.00%)	3 / 64 (4.69%)
occurrences (all)	5	0	4
Hypocalcaemia			
subjects affected / exposed	4 / 104 (3.85%)	1 / 52 (1.92%)	3 / 64 (4.69%)
occurrences (all)	4	1	9
Hyponatraemia			
subjects affected / exposed	4 / 104 (3.85%)	2 / 52 (3.85%)	2 / 64 (3.13%)
occurrences (all)	5	2	2
Hypophosphataemia			
subjects affected / exposed	1 / 104 (0.96%)	0 / 52 (0.00%)	1 / 64 (1.56%)
occurrences (all)	1	0	1

Non-serious adverse events	BAT to MMB		
Total subjects affected by non-serious adverse events subjects affected / exposed	40 / 40 (100.00%)		
Vascular disorders hypertension subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2		
Hypotension subjects affected / exposed occurrences (all)	4 / 40 (10.00%) 5		
Haematoma subjects affected / exposed occurrences (all)	4 / 40 (10.00%) 4		
General disorders and administration site conditions Ascites subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2		
Asthenia subjects affected / exposed occurrences (all)	11 / 40 (27.50%) 20		
Fatigue subjects affected / exposed occurrences (all)	7 / 40 (17.50%) 9		
Pyrexia subjects affected / exposed occurrences (all)	10 / 40 (25.00%) 13		
Oedema peripheral subjects affected / exposed occurrences (all)	6 / 40 (15.00%) 6		
Early satiety subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1		
Chills subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2		
Respiratory, thoracic and mediastinal			

disorders Cough subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all) Epistaxis subjects affected / exposed occurrences (all) Pneumonitis subjects affected / exposed occurrences (all) Pulmonary oedema subjects affected / exposed occurrences (all)	 8 / 40 (20.00%) 17 6 / 40 (15.00%) 9 2 / 40 (5.00%) 3 2 / 40 (5.00%) 2 2 / 40 (5.00%) 2		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	 3 / 40 (7.50%) 3		
Investigations Weight decreased subjects affected / exposed occurrences (all) Blood creatinine increased subjects affected / exposed occurrences (all)	 5 / 40 (12.50%) 6 1 / 40 (2.50%) 1		
Injury, poisoning and procedural complications Contusion subjects affected / exposed occurrences (all) Fall subjects affected / exposed occurrences (all) Procedural pain	 2 / 40 (5.00%) 2 2 / 40 (5.00%) 2		

subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2		
Cardiac disorders Cardiac failure subjects affected / exposed occurrences (all)	 2 / 40 (5.00%) 2		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Paraesthesia subjects affected / exposed occurrences (all) Peripheral sensory neuropathy subjects affected / exposed occurrences (all) Somnolence subjects affected / exposed occurrences (all)	 6 / 40 (15.00%) 7 6 / 40 (15.00%) 10 3 / 40 (7.50%) 3 7 / 40 (17.50%) 8 3 / 40 (7.50%) 3		
Blood and lymphatic system disorders Thrombocytopenia subjects affected / exposed occurrences (all) Anaemia subjects affected / exposed occurrences (all) Neutropenia subjects affected / exposed occurrences (all) Splenomegaly subjects affected / exposed occurrences (all) Leukocytosis	 11 / 40 (27.50%) 17 6 / 40 (15.00%) 6 3 / 40 (7.50%) 3 1 / 40 (2.50%) 3		

subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	3		
Eye disorders			
Dry eye			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	3		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	10 / 40 (25.00%)		
occurrences (all)	13		
Nausea			
subjects affected / exposed	5 / 40 (12.50%)		
occurrences (all)	6		
Abdominal pain			
subjects affected / exposed	5 / 40 (12.50%)		
occurrences (all)	5		
Constipation			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Dyspepsia			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Abdominal pain upper			
subjects affected / exposed	4 / 40 (10.00%)		
occurrences (all)	4		
Vomiting			
subjects affected / exposed	4 / 40 (10.00%)		
occurrences (all)	4		
Abdominal distension			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Dry mouth			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Melaena			

subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	3		
Dysphagia			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Abdominal wall haematoma			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	4		
Night sweats			
subjects affected / exposed	6 / 40 (15.00%)		
occurrences (all)	7		
Hyperhidrosis			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	3		
Alopecia			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Dry skin			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	4		
Dysuria			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Renal failure			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Urinary incontinence			

subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Back pain			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	4		
Pain in extremity			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Bone pain			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	3		
Muscle spasms			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	8 / 40 (20.00%)		
occurrences (all)	16		
Upper respiratory tract infection			
subjects affected / exposed	5 / 40 (12.50%)		
occurrences (all)	5		
Oral herpes			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Bronchitis			
subjects affected / exposed	4 / 40 (10.00%)		
occurrences (all)	4		
Nasopharyngitis			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Pneumonia			

subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	4		
Oral candidiasis			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	3		
Decreased appetite			
subjects affected / exposed	5 / 40 (12.50%)		
occurrences (all)	7		
Vitamin B1 deficiency			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Hyperuricaemia			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	3		
Hypokalaemia			
subjects affected / exposed	4 / 40 (10.00%)		
occurrences (all)	5		
Hypocalcaemia			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Hyponatraemia			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	3		
Hypophosphataemia			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/29275119