



Clinical trial results:

A Phase 3, Randomized Study to Evaluate the Efficacy of Mometotinib 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 |

| 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 inter-quartile range (Q1-Q3) | 75.0 66.0 to 85.7 | | |
| Height Units: cm median inter-quartile range (Q1-Q3) | 170.0 162.5 to 176.0 | | |
| Body Mass Index Units: kg/m ² median inter-quartile range (Q1-Q3) | 26.0 23.6 to 28.6 | | |
| Hemoglobin Units: g/dL median inter-quartile range (Q1-Q3) | 9.0 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 $\geq 35\%$ 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 $\geq 35\%$ 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 $\geq 50\%$ 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 $\geq 50\%$ 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 $\geq 50\%$ 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 occurrences (all) | 3 / 104 (2.88%) 4 | 6 / 52 (11.54%) 6 | 2 / 64 (3.13%) 2 |
| Chills subjects affected / exposed occurrences (all) | 2 / 104 (1.92%) 3 | 0 / 52 (0.00%) 0 | 2 / 64 (3.13%) 2 |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 18 / 104 (17.31%) 22 | 6 / 52 (11.54%) 7 | 17 / 64 (26.56%) 27 |
| Dyspnoea subjects affected / exposed occurrences (all) | 12 / 104 (11.54%) 18 | 7 / 52 (13.46%) 7 | 5 / 64 (7.81%) 5 |
| Epistaxis subjects affected / exposed occurrences (all) | 8 / 104 (7.69%) 9 | 6 / 52 (11.54%) 9 | 2 / 64 (3.13%) 2 |
| Pneumonitis subjects affected / exposed occurrences (all) | 0 / 104 (0.00%) 0 | 0 / 52 (0.00%) 0 | 1 / 64 (1.56%) 1 |
| Pulmonary oedema subjects affected / exposed occurrences (all) | 0 / 104 (0.00%) 0 | 0 / 52 (0.00%) 0 | 0 / 64 (0.00%) 0 |
| Psychiatric disorders Insomnia subjects affected / exposed occurrences (all) | 3 / 104 (2.88%) 3 | 4 / 52 (7.69%) 4 | 4 / 64 (6.25%) 4 |
| Investigations Weight decreased subjects affected / exposed occurrences (all) | 10 / 104 (9.62%) 10 | 3 / 52 (5.77%) 3 | 7 / 64 (10.94%) 7 |
| Blood creatinine increased subjects affected / exposed occurrences (all) | 6 / 104 (5.77%) 7 | 0 / 52 (0.00%) 0 | 5 / 64 (7.81%) 5 |
| Injury, poisoning and procedural complications Contusion | | | |

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

| | | | |
|---|-------------------------|-----------------------|------------------------|
| subjects affected / exposed occurrences (all) | 7 / 104 (6.73%) 10 | 1 / 52 (1.92%) 3 | 2 / 64 (3.13%) 4 |
| Splenomegaly subjects affected / exposed occurrences (all) | 2 / 104 (1.92%) 3 | 3 / 52 (5.77%) 3 | 1 / 64 (1.56%) 1 |
| Leukocytosis subjects affected / exposed occurrences (all) | 1 / 104 (0.96%) 1 | 0 / 52 (0.00%) 0 | 5 / 64 (7.81%) 5 |
| Eye disorders Dry eye subjects affected / exposed occurrences (all) | 0 / 104 (0.00%) 0 | 0 / 52 (0.00%) 0 | 0 / 64 (0.00%) 0 |
| Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) | 33 / 104 (31.73%) 42 | 8 / 52 (15.38%) 16 | 19 / 64 (29.69%) 26 |
| Nausea subjects affected / exposed occurrences (all) | 20 / 104 (19.23%) 25 | 5 / 52 (9.62%) 6 | 8 / 64 (12.50%) 10 |
| Abdominal pain subjects affected / exposed occurrences (all) | 16 / 104 (15.38%) 22 | 7 / 52 (13.46%) 9 | 7 / 64 (10.94%) 14 |
| Constipation subjects affected / exposed occurrences (all) | 11 / 104 (10.58%) 15 | 2 / 52 (3.85%) 2 | 5 / 64 (7.81%) 7 |
| Dyspepsia subjects affected / exposed occurrences (all) | 10 / 104 (9.62%) 10 | 1 / 52 (1.92%) 1 | 2 / 64 (3.13%) 2 |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 8 / 104 (7.69%) 8 | 1 / 52 (1.92%) 1 | 2 / 64 (3.13%) 2 |
| Vomiting subjects affected / exposed occurrences (all) | 7 / 104 (6.73%) 7 | 1 / 52 (1.92%) 1 | 5 / 64 (7.81%) 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 occurrences (all) | 5 / 104 (4.81%) 5 | 2 / 52 (3.85%) 3 | 6 / 64 (9.38%) 6 |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 4 / 104 (3.85%) 4 | 2 / 52 (3.85%) 3 | 3 / 64 (4.69%) 3 |
| Pneumonia subjects affected / exposed occurrences (all) | 1 / 104 (0.96%) 1 | 0 / 52 (0.00%) 0 | 4 / 64 (6.25%) 4 |
| Oral candidiasis subjects affected / exposed occurrences (all) | 2 / 104 (1.92%) 2 | 1 / 52 (1.92%) 1 | 0 / 64 (0.00%) 0 |
| Metabolism and nutrition disorders | | | |
| Hyperkalaemia subjects affected / exposed occurrences (all) | 8 / 104 (7.69%) 8 | 1 / 52 (1.92%) 1 | 5 / 64 (7.81%) 6 |
| Decreased appetite subjects affected / exposed occurrences (all) | 7 / 104 (6.73%) 8 | 2 / 52 (3.85%) 2 | 4 / 64 (6.25%) 5 |
| Vitamin B1 deficiency subjects affected / exposed occurrences (all) | 7 / 104 (6.73%) 7 | 2 / 52 (3.85%) 2 | 6 / 64 (9.38%) 6 |
| Hyperuricaemia subjects affected / exposed occurrences (all) | 6 / 104 (5.77%) 7 | 2 / 52 (3.85%) 2 | 4 / 64 (6.25%) 5 |
| Hypokalaemia subjects affected / exposed occurrences (all) | 4 / 104 (3.85%) 5 | 0 / 52 (0.00%) 0 | 3 / 64 (4.69%) 4 |
| Hypocalcaemia subjects affected / exposed occurrences (all) | 4 / 104 (3.85%) 4 | 1 / 52 (1.92%) 1 | 3 / 64 (4.69%) 9 |
| Hyponatraemia subjects affected / exposed occurrences (all) | 4 / 104 (3.85%) 5 | 2 / 52 (3.85%) 2 | 2 / 64 (3.13%) 2 |
| Hypophosphataemia subjects affected / exposed occurrences (all) | 1 / 104 (0.96%) 1 | 0 / 52 (0.00%) 0 | 1 / 64 (1.56%) 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 | 2 / 40 (5.00%) | | |
| occurrences (all) | 2 | | |
| Hypotension | | | |
| subjects affected / exposed | 4 / 40 (10.00%) | | |
| occurrences (all) | 5 | | |
| Haematoma | | | |
| subjects affected / exposed | 4 / 40 (10.00%) | | |
| occurrences (all) | 4 | | |
| General disorders and administration site conditions | | | |
| Ascites | | | |
| subjects affected / exposed | 2 / 40 (5.00%) | | |
| occurrences (all) | 2 | | |
| Asthenia | | | |
| subjects affected / exposed | 11 / 40 (27.50%) | | |
| occurrences (all) | 20 | | |
| Fatigue | | | |
| subjects affected / exposed | 7 / 40 (17.50%) | | |
| occurrences (all) | 9 | | |
| Pyrexia | | | |
| subjects affected / exposed | 10 / 40 (25.00%) | | |
| occurrences (all) | 13 | | |
| Oedema peripheral | | | |
| subjects affected / exposed | 6 / 40 (15.00%) | | |
| occurrences (all) | 6 | | |
| Early satiety | | | |
| subjects affected / exposed | 1 / 40 (2.50%) | | |
| occurrences (all) | 1 | | |
| Chills | | | |
| subjects affected / exposed | 2 / 40 (5.00%) | | |
| occurrences (all) | 2 | | |
| Respiratory, thoracic and mediastinal | | | |

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

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