Clinical trial results:
Open-label Study to Assess the Long-term Safety and Efficacy of Momelotinib in Subjects with Primary Myelofibrosis, Post-polycythemia Vera Myelofibrosis, Post-essential Thrombocythemia Myelofibrosis, Polycythemia Vera or Essential Thrombocythemia

Summary

EudraCT number	2013-004476-36
Trial protocol	DE
Global end of trial date	06 December 2018

Results information

Result version number	v1 (current)
This version publication date	14 June 2020
First version publication date	14 June 2020
Summary attachment (see zip file)	GS-US-352-1154 Final CSR Synopsis (GS-US-352-1154 Final CSR synopsis.pdf)

Trial information

Trial identification

Sponsor protocol code	GS-US-352-1154

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02124746
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Sierra Oncology, Inc.
Sponsor organisation address	46701 Commerce Center Drive, Plymouth, United States,
Public contact	Dr. Barbara Klencke, Sierra Oncology, Inc., bklencke@sierraoncology.com
Scientific contact	Dr. Barbara Klencke, Sierra Oncology, Inc., bklencke@sierraoncology.com
Sponsor organisation name	Gilead Sciences International Ltd.
Sponsor organisation address	333 Lakeside Drive, Foster City, United States,
Public contact	Clinical Trials Mailbox,, Gilead Sciences International Ltd., clinical.trials@gilead.com
Scientific contact	Clinical Trials Mailbox,, Gilead Sciences International Ltd., clinical.trials@gilead.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	21 January 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 December 2018
Global end of trial reached?	Yes
Global end of trial date	06 December 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this extension study was to determine long-term safety and tolerability of momelotinib (MMB) in 4 cohorts:
• Cohort 1: Subjects who received MMB capsules in Study CCL09101E for primary myelofibrosis (PMF), post-polycythemia vera (PV) myelofibrosis (MF), and post essential thrombocythemia (ET) MF without documented progressive disease.
• Cohort 2: Subjects who received MMB capsules in Study YM387-II-02 for PMF, post PV/ET MF without documented progressive disease.
• Cohort 3: Subjects who received MMB tablets in Study GS-US-354-0101 for PV or ET who completed 24 weeks of treatment and whose disease had not progressed on study.
• Cohort 4: Subjects who received MMB tablets in Study GS-US-352-1672 for PMF, post-PV MF, and post-ET MF, who completed 24 weeks of treatment in Study GS-US-352-1672 and responded to treatment while on study.

Cohort 3 was discontinued due to limited efficacy of MMB in the treatment of PV and ET in Study GS-US-354-0101.

Protection of trial subjects:

The protocol, protocol amendments, consent forms, and administrative letters 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 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. This study was conducted in accordance with recognized international scientific and ethical standards, including but not limited to the International Council for Harmonization (ICH) guideline for Good Clinical Practice (GCP) and the original principles embodied in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 May 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	United States: 68

Country: Number of subjects enrolled	Australia: 3
Country: Number of subjects enrolled	Canada: 13
Worldwide total number of subjects	87
EEA total number of subjects	3

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	40
From 65 to 84 years	46
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Benefiting subjects enrolled in select prior MMB studies (parent studies) were included for continued administration of MMB. Cohort 3 (PV/ET; n=13) was closed and subjects were discontinued due to limited efficacy of MMB in the treatment of PV/ET observed in the parent study.

Cohort 3 was excluded from safety and efficacy analyses.

Pre-assignment

Screening details:

Procedures performed at a regular follow-up visit in the subject's parent MMB study could be used to fulfill screening criteria and to establish any new medical history for this extension study.

Period 1

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

Arms

Arm title	Rollover Safety Analysis Set (RSAS)

Arm description:

The Rollover Safety Analysis Set as defined in the statistical analysis plan included all subjects with MF (ie, Cohorts 1, 2 and 4) who were enrolled in Study GS-US-352-1154. This analysis set was used for demographic and baseline characteristics, study treatment administration and compliance, safety and efficacy analyses.

Subjects enrolled in Cohort 3 (non-MF subjects) were excluded in the analysis sets as the cohort was discontinued due to limited efficacy in the parent study.

Of note, 19 subjects in Study GS-US-352-1154 were transitioned to a separate extended access study (SRA-MMB-4365) to continue MMB treatment. These 19 subjects include 13 subjects who completed 48 months or more of the allowed MMB therapy on Study GS-US-352-1154 and 6 additional subjects who were transferred into Study SRA-MMB-4365 prior to reaching Month 48 so that GS-US-352-1154 could be terminated by the sponsor.

Arm type	Experimental
Investigational medicinal product name	momelotinib (MMB)
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 1[1]	Rollover Safety Analysis Set (RSAS)
Started	74
Completed	15
Not completed	59
Physician decision	15

Consent withdrawn by subject	6
Disease progression	13
Adverse event, non-fatal	5
Death	6
Non-compliance with study drug	1
Study Terminated by Sponsor	6
Lack of efficacy	7

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The study enrolled subjects in 4 cohorts. One of the cohorts, Cohort 3, consisted of 13 patients who received MMB in Study GS-US-354-0101 for the treatment of PV and ET. Per Amendment 3, Cohort 3 was closed, and all enrolled subjects were discontinued from Study GS-US-352-1154 due to limited efficacy of MMB in the treatment of PV and ET in parent study GS-US-354-0101.

All analyses were performed excluding this cohort of non-MF subjects.

Baseline characteristics

Reporting groups

Reporting group title	Rollover Safety Analysis Set (RSAS)

Reporting group description:

The Rollover Safety Analysis Set as defined in the statistical analysis plan included all subjects with MF (ie, Cohorts 1, 2 and 4) who were enrolled in Study GS-US-352-1154. This analysis set was used for demographic and baseline characteristics, study treatment administration and compliance, safety and efficacy analyses.

Subjects enrolled in Cohort 3 (non-MF subjects) were excluded in the analysis sets as the cohort was discontinued due to limited efficacy in the parent study.

Of note, 19 subjects in Study GS-US-352-1154 were transitioned to a separate extended access study (SRA-MMB-4365) to continue MMB treatment. These 19 subjects include 13 subjects who completed 48 months or more of the allowed MMB therapy on Study GS-US-352-1154 and 6 additional subjects who were transferred into Study SRA-MMB-4365 prior to reaching Month 48 so that GS-US-352-1154 could be terminated by the sponsor.

Reporting group values	Rollover Safety Analysis Set (RSAS)	Total	
Number of subjects	74	74	
Age categorical Units: Subjects			
Adults (18-64 years)	34	34	
From 65-84 years	39	39	
85 years and over	1	1	
Age continuous Units: years			
median	66.5		
full range (min-max)	34.0 to 88.0	-	
Gender categorical Units: Subjects			
Female	36	36	
Male	38	38	
Transfusion Dependent at Baseline Units: Subjects			
Yes	36	36	
No	35	35	
Missing	3	3	

End points

End points reporting groups

Reporting group title	Rollover Safety Analysis Set (RSAS)

Reporting group description:

The Rollover Safety Analysis Set as defined in the statistical analysis plan included all subjects with MF (ie, Cohorts 1, 2 and 4) who were enrolled in Study GS-US-352-1154. This analysis set was used for demographic and baseline characteristics, study treatment administration and compliance, safety and efficacy analyses.

Subjects enrolled in Cohort 3 (non-MF subjects) were excluded in the analysis sets as the cohort was discontinued due to limited efficacy in the parent study.

Of note, 19 subjects in Study GS-US-352-1154 were transitioned to a separate extended access study (SRA-MMB-4365) to continue MMB treatment. These 19 subjects include 13 subjects who completed 48 months or more of the allowed MMB therapy on Study GS-US-352-1154 and 6 additional subjects who were transferred into Study SRA-MMB-4365 prior to reaching Month 48 so that GS-US-352-1154 could be terminated by the sponsor.

Primary: Long Term Safety and Tolerability as Measured by the Incidence and Severity of Adverse Events and Clinical Laboratory Abnormalities

End point title	Long Term Safety and Tolerability as Measured by the Incidence and Severity of Adverse Events and Clinical Laboratory Abnormalities[1]

End point description:

Long-term safety and tolerability profile of MMB based on safety data (adverse events and selected hematology and chemistry laboratory parameters) collected after the first dose of MMB in the parent study.

End point type	Primary

End point timeframe:

From the first dose of MMB in the parent study to 30 days following permanent discontinuation of MMB in Study GS-US-352-1154.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Due to the nature of this endpoint, a statistical analysis was not conducted.

End point values	Rollover Safety Analysis Set (RSAS)			
Subject group type	Reporting group			
Number of subjects analysed	74			
Units: subjects				
Subjects with at least one AE (any grade)	73			
Subjects with at least one Grade 3 or higher AE	62			
Subjects with Grade 3 lab toxicity (highest grade)	36			
Subjects with Grade 4 lab toxicity (highest grade)	16			

Statistical analyses

No statistical analyses for this end point

Secondary: Splenic Response Rate

End point title	Splenic Response Rate

End point description:

The proportion of subjects achieving a spleen response, defined as a reduction of 50% or more in palpable splenomegaly of a spleen that was at least 10 cm below the LCM at baseline, or a spleen that was palpable at > 5 cm and < 10 cm below the LCM at baseline becoming not palpable for at least 56 days, using baseline of the parent study as the reference.

End point type	Secondary

End point timeframe:

From baseline in the parent study until the last spleen assessment in Study GS-US-352-1154, up to 30 days following permanent discontinuation of MMB.

End point values	Rollover Safety Analysis Set (RSAS)			
Subject group type	Reporting group			
Number of subjects analysed	63[2]			
Units: percentage of subjects				
number (not applicable)				
Spleen response rate	71.4			

Notes:

[2] - There were 63 RSAS subjects with splenomegaly >5 cm at baseline in the parent studies.

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Splenic Response

End point title	Duration of Splenic Response

End point description:

The interval from the first onset of splenic response (in the parent study or Study GS-US-352-1154) to the earliest date of loss of splenic response. Loss of response was defined as the reduction of splenomegaly by < 50% among responders (with splenomegaly ≥ 10 cm below the LCM at baseline) that lasts ≥ 56 days, or the recurrence of > 0 cm splenomegaly among responders (with splenomegaly > 5 and < 10 cm at baseline) that lasts ≥ 56 days.

Duration of splenic response was measured by descriptive statistics. Data from responders who maintained their response was censored at the last assessment date.

End point type	Secondary

End point timeframe:

From baseline in the parent study until the last spleen assessment in Study GS-US-352-1154, up to 30 days following permanent discontinuation of MMB.

End point values	Rollover Safety Analysis Set (RSAS)			
Subject group type	Reporting group			
Number of subjects analysed	45[3]			
Units: days				
median (inter-quartile range (Q1-Q3))	990.00 (226.00 to 1802.00)			

Notes:

[3] - There were 45 spleen responders.

Statistical analyses

No statistical analyses for this end point

Secondary: Transfusion Independence Response Rate

End point title	Transfusion Independence Response Rate

End point description:

The proportion of transfusion dependent subjects at entry to a parent study who became transfusion-independent for ≥ 12 weeks at any time from the first dose of MMB in the parent study until the end of Study GS-US-352-1154.

End point type	Secondary

End point timeframe:

From baseline in the parent study until the last assessment in Study GS-US-352-1154, up to 30 days following permanent discontinuation of MMB.

End point values	Rollover Safety Analysis Set (RSAS)			
Subject group type	Reporting group			
Number of subjects analysed	36[4]			
Units: percentage of subjects				
number (not applicable)				
Transfusion independence response rate	77.8			

Notes:

[4] - There were 36 RSAS subjects who were transfusion dependent at baseline in the parent studies.

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Transfusion Independence Response

End point title	Duration of Transfusion Independence Response

End point description:

The interval from the first onset date of transfusion independence (in the parent study or Study GS-US-352-1154) to the earliest date of loss of response for participants who are transfusion dependent at baseline in the parent study. Loss of TI response was defined as receiving an RBC transfusion after achieving a TI response.

Duration of transfusion independence response was measured by descriptive statistics. Data from responders who maintained their response was censored at the last assessment date.

End point type	Secondary

End point timeframe:

From baseline in the parent study until the last assessment date in Study GS-US-352-1154, up to 30 days following permanent discontinuation of MMB.

End point values	Rollover Safety Analysis Set (RSAS)			
Subject group type	Reporting group			
Number of subjects analysed	28[5]			
Units: days				
median (inter-quartile range (Q1-Q3))	193.50 (110.00 to 701.00)			

Notes:

[5] - There were 28 transfusion independence responders.

Statistical analyses

No statistical analyses for this end point

Secondary: Anemia Response Rate

End point title	Anemia Response Rate

End point description:

The proportion of subjects achieving an anemia response, defined as:
• Achieving transfusion independence for ≥ 12 weeks, for subjects who were transfusion-dependent at baseline in the parent study, or
• Having ≥ 2 g/dL increase in Hgb from baseline for ≥ 12 weeks, for subjects with Hgb < 10 g/dL at baseline in the parent study who were not transfusion-dependent (Cohort 1) or who were transfusion-independent (Cohort 2).

End point type	Secondary

End point timeframe:

From baseline in the parent study until the last assessment in Study GS-US-352-1154, up to 30 days following permanent discontinuation of MMB.

End point values	Rollover Safety Analysis Set (RSAS)			
Subject group type	Reporting group			
Number of subjects analysed	52[6]			
Units: percentage of subjects				
number (not applicable)				
Anemia response rate	67.3			

Notes:

[6] - There were 52 RSAS subjects who were anemia response-evaluable at baseline in the parent studies.

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Anemia Response

End point title	Duration of Anemia Response

End point description:

The interval from the first onset of anemia response (in the parent study or Study GS-US-352-1154) to the earliest date of loss of anemia response. Loss of anemia response was defined as having any RBC transfusion after achieving an anemia response.

Duration of anemia response was measured by descriptive statistics. Data from responders who maintained their response was censored at the last assessment date.

End point type	Secondary

End point timeframe:

From baseline in the parent study until the last assessment in Study GS-US-352-1154, up to 30 days following permanent discontinuation of MMB.

End point values	Rollover Safety Analysis Set (RSAS)			
Subject group type	Reporting group			
Number of subjects analysed	35[7]			
Units: days				
median (inter-quartile range (Q1-Q3))	358.00 (114.0 to 954.00)			

Notes:

[7] - There were 35 anemia responders.

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of RBC Transfusion

End point title	Rate of RBC Transfusion

End point description:

The average number of RBC units per subject month during the parent study and/or Study GS-US-352-1154.

End point type	Secondary

End point timeframe:

From the first dose of MMB in the parent study until the last dose of MMB in Study GS-US-352-1154.

End point values	Rollover Safety Analysis Set (RSAS)			
Subject group type	Reporting group			
Number of subjects analysed	74			
Units: RBC units per month				
median (full range (min-max))				
Rate in Parent Studies	0.08 (0.0 to 5.4)			

Rate in Study GS-US-352-1154	0.00 (0.0 to 4.8)			
Rate Since First Dose of MMB in Parent Studies	0.06 (0.0 to 4.9)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first dose of MMB in the parent study until 30 days following permanent discontinuation of MMB in Study GS-US-352-1154.

Adverse event reporting additional description:

Occurrences may be counted multiple times, since within a given subject, individual grade or causality changes may be recorded. In addition, distinct verbatim terms that are coded to a single preferred term are also counted as separate occurrences.

Per protocol, disease progression AEs assessed as unrelated to MMB were not captured as serious.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	Rollover Safety Analysis Set

Reporting group description:

The Rollover Safety Analysis Set (RSAS) as defined in the SAP included all subjects with MF (ie, Cohorts 1, 2 and 4) who were enrolled in Study GS-US-352-1154. This analysis set was used for demographic and baseline characteristics, study treatment administration and compliance, safety and efficacy analyses.

Subjects enrolled in Cohort 3 (non-MF subjects) were excluded in the analysis sets as the cohort was discontinued due to limited efficacy in the parent study.

Serious adverse events	Rollover Safety Analysis Set		
Total subjects affected by serious adverse events			
subjects affected / exposed	49 / 74 (66.22%)		
number of deaths (all causes)	8		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
ADENOCARCINOMA OF COLON			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
MANTLE CELL LYMPHOMA			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
NON-HODGKIN'S LYMPHOMA			

subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
OVARIAN CANCER				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
DEEP VEIN THROMBOSIS				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
HYPOTENSION				
subjects affected / exposed	2 / 74 (2.70%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
THROMBOSIS				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
ASTHENIA				
subjects affected / exposed	2 / 74 (2.70%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
CHEST PAIN				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
DEATH				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			

PAIN				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
PYREXIA				
subjects affected / exposed	2 / 74 (2.70%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
DYSPNOEA				
subjects affected / exposed	3 / 74 (4.05%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
PULMONARY EMBOLISM				
subjects affected / exposed	3 / 74 (4.05%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
DELIRIUM				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Investigations				
BLOOD CREATININE INCREASED				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
EJECTION FRACTION DECREASED				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
CRANIOCEREBRAL INJURY				

subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
FALL				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
SUBDURAL HAEMATOMA				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
TENDON INJURY				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
TIBIA FRACTURE				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
ANGINA PECTORIS				
subjects affected / exposed	2 / 74 (2.70%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
AORTIC VALVE DISEASE				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
ATRIAL FIBRILLATION				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
ATRIAL FLUTTER				

subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
ATRIOVENTRICULAR BLOCK				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
CARDIAC FAILURE				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
CARDIAC FAILURE ACUTE				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
CARDIAC FAILURE CONGESTIVE				
subjects affected / exposed	4 / 74 (5.41%)			
occurrences causally related to treatment / all	1 / 5			
deaths causally related to treatment / all	0 / 1			
CARDIOMYOPATHY				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
MYOCARDIAL INFARCTION				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
MYOCARDIAL ISCHAEMIA				
subjects affected / exposed	2 / 74 (2.70%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
PALPITATIONS				

subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
SINUS NODE DYSFUNCTION				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
VENTRICULAR TACHYCARDIA				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
CEREBRAL HAEMORRHAGE				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
DIZZINESS				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
INTRACRANIAL VENOUS SINUS THROMBOSIS				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
ISCHAEMIC STROKE				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
SYNCOPE				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
TRANSIENT GLOBAL AMNESIA				

subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
WERNICKE'S ENCEPHALOPATHY			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
FEBRILE NEUTROPENIA			
subjects affected / exposed	2 / 74 (2.70%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
NEUTROPENIA			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
THROMBOCYTOPENIA			
subjects affected / exposed	2 / 74 (2.70%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	6 / 74 (8.11%)		
occurrences causally related to treatment / all	1 / 6		
deaths causally related to treatment / all	0 / 0		
ASCITES			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
COLITIS			

subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
CONSTIPATION				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
DIARRHOEA				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
GASTROINTESTINAL HAEMORRHAGE				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
HAEMATOCHEZIA				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
MOUTH HAEMORRHAGE				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
SALIVARY GLAND ENLARGEMENT				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
SMALL INTESTINAL OBSTRUCTION				
subjects affected / exposed	2 / 74 (2.70%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
VARICES OESOPHAGEAL				

subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
CHOLECYSTITIS CHRONIC			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
HYPERHIDROSIS			
subjects affected / exposed	1 / 74 (1.35%)		
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	5 / 74 (6.76%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
HAEMATURIA			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
NEPHROLITHIASIS			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
PROTEINURIA			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			

subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
BACK PAIN				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
BONE PAIN				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
MUSCULAR WEAKNESS				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
MYALGIA				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
APPENDICITIS				
subjects affected / exposed	2 / 74 (2.70%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
BACTERIAL INFECTION				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
BRONCHITIS				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
CELLULITIS				

subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
CLOSTRIDIUM DIFFICILE COLITIS				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
GASTROENTERITIS				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
GASTROENTERITIS ESCHERICHIA COLI				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
INFECTION				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
LOCALISED INFECTION				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
LUNG INFECTION				
subjects affected / exposed	4 / 74 (5.41%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 1			
PERITONITIS				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
PHARYNGITIS				

subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
PNEUMOCOCCAL SEPSIS				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
PNEUMONIA				
subjects affected / exposed	7 / 74 (9.46%)			
occurrences causally related to treatment / all	3 / 8			
deaths causally related to treatment / all	0 / 0			
PNEUMONIA KLEBSIELLA				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
PNEUMONIA PNEUMOCOCCAL				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
PYELONEPHRITIS				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
RESPIRATORY SYNCYTIAL VIRUS INFECTION				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
SEPSIS				
subjects affected / exposed	3 / 74 (4.05%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 1			
SINUSITIS BACTERIAL				

subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
SYSTEMIC MYCOSIS				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
UPPER RESPIRATORY TRACT INFECTION				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
URINARY TRACT INFECTION				
subjects affected / exposed	3 / 74 (4.05%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
DEHYDRATION				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
HYPOKALAEMIA				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
METABOLIC ACIDOSIS				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

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

Non-serious adverse events	Rollover Safety Analysis Set		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	73 / 74 (98.65%)		
Vascular disorders			
FLUSHING			
subjects affected / exposed	8 / 74 (10.81%)		
occurrences (all)	9		
HAEMATOMA			
subjects affected / exposed	5 / 74 (6.76%)		
occurrences (all)	8		
HYPERTENSION			
subjects affected / exposed	14 / 74 (18.92%)		
occurrences (all)	16		
HYPOTENSION			
subjects affected / exposed	16 / 74 (21.62%)		
occurrences (all)	19		
Surgical and medical procedures			
TOOTH EXTRACTION			
subjects affected / exposed	5 / 74 (6.76%)		
occurrences (all)	6		
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	5 / 74 (6.76%)		
occurrences (all)	5		
CHEST PAIN			
subjects affected / exposed	7 / 74 (9.46%)		
occurrences (all)	7		
CHILLS			
subjects affected / exposed	4 / 74 (5.41%)		
occurrences (all)	5		
FATIGUE			
subjects affected / exposed	35 / 74 (47.30%)		
occurrences (all)	55		
INFLUENZA LIKE ILLNESS			
subjects affected / exposed	4 / 74 (5.41%)		
occurrences (all)	5		

OEDEMA PERIPHERAL			
subjects affected / exposed	19 / 74 (25.68%)		
occurrences (all)	26		
PAIN			
subjects affected / exposed	6 / 74 (8.11%)		
occurrences (all)	6		
PYREXIA			
subjects affected / exposed	16 / 74 (21.62%)		
occurrences (all)	22		
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	21 / 74 (28.38%)		
occurrences (all)	33		
DYSPNOEA			
subjects affected / exposed	29 / 74 (39.19%)		
occurrences (all)	42		
DYSPNOEA EXERTIONAL			
subjects affected / exposed	4 / 74 (5.41%)		
occurrences (all)	4		
EPISTAXIS			
subjects affected / exposed	5 / 74 (6.76%)		
occurrences (all)	15		
NASAL CONGESTION			
subjects affected / exposed	4 / 74 (5.41%)		
occurrences (all)	5		
OROPHARYNGEAL PAIN			
subjects affected / exposed	7 / 74 (9.46%)		
occurrences (all)	7		
PRODUCTIVE COUGH			
subjects affected / exposed	4 / 74 (5.41%)		
occurrences (all)	5		
SINUS CONGESTION			
subjects affected / exposed	4 / 74 (5.41%)		
occurrences (all)	4		
Psychiatric disorders			

ANXIETY			
subjects affected / exposed	4 / 74 (5.41%)		
occurrences (all)	4		
DEPRESSION			
subjects affected / exposed	7 / 74 (9.46%)		
occurrences (all)	7		
INSOMNIA			
subjects affected / exposed	13 / 74 (17.57%)		
occurrences (all)	13		
Investigations			
ACTIVATED PARTIAL THROMBOPLASTIN TIME PROLONGED			
subjects affected / exposed	5 / 74 (6.76%)		
occurrences (all)	7		
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	19 / 74 (25.68%)		
occurrences (all)	35		
AMYLASE INCREASED			
subjects affected / exposed	12 / 74 (16.22%)		
occurrences (all)	30		
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	11 / 74 (14.86%)		
occurrences (all)	27		
BLOOD ALKALINE PHOSPHATASE INCREASED			
subjects affected / exposed	5 / 74 (6.76%)		
occurrences (all)	12		
BLOOD BILIRUBIN INCREASED			
subjects affected / exposed	8 / 74 (10.81%)		
occurrences (all)	15		
BLOOD CREATININE INCREASED			
subjects affected / exposed	17 / 74 (22.97%)		
occurrences (all)	29		
BLOOD URIC ACID INCREASED			
subjects affected / exposed	4 / 74 (5.41%)		
occurrences (all)	4		

ELECTROCARDIOGRAM QT PROLONGED			
subjects affected / exposed	4 / 74 (5.41%)		
occurrences (all)	8		
GAMMA-GLUTAMYLTRANSFERASE INCREASED			
subjects affected / exposed	4 / 74 (5.41%)		
occurrences (all)	7		
INTERNATIONAL NORMALISED RATIO INCREASED			
subjects affected / exposed	5 / 74 (6.76%)		
occurrences (all)	8		
LIPASE INCREASED			
subjects affected / exposed	15 / 74 (20.27%)		
occurrences (all)	21		
LYMPHOCYTE COUNT DECREASED			
subjects affected / exposed	4 / 74 (5.41%)		
occurrences (all)	4		
NEUTROPHIL COUNT DECREASED			
subjects affected / exposed	5 / 74 (6.76%)		
occurrences (all)	14		
PLATELET COUNT DECREASED			
subjects affected / exposed	11 / 74 (14.86%)		
occurrences (all)	32		
WEIGHT DECREASED			
subjects affected / exposed	8 / 74 (10.81%)		
occurrences (all)	11		
WEIGHT INCREASED			
subjects affected / exposed	4 / 74 (5.41%)		
occurrences (all)	4		
WHITE BLOOD CELL COUNT DECREASED			
subjects affected / exposed	5 / 74 (6.76%)		
occurrences (all)	22		
Injury, poisoning and procedural complications			
CONTUSION			
subjects affected / exposed	22 / 74 (29.73%)		
occurrences (all)	32		

FALL			
subjects affected / exposed	8 / 74 (10.81%)		
occurrences (all)	10		
FOOT FRACTURE			
subjects affected / exposed	4 / 74 (5.41%)		
occurrences (all)	4		
Cardiac disorders			
ATRIAL FIBRILLATION			
subjects affected / exposed	4 / 74 (5.41%)		
occurrences (all)	4		
PERICARDIAL EFFUSION			
subjects affected / exposed	4 / 74 (5.41%)		
occurrences (all)	4		
SINUS BRADYCARDIA			
subjects affected / exposed	7 / 74 (9.46%)		
occurrences (all)	10		
Nervous system disorders			
DIZZINESS			
subjects affected / exposed	28 / 74 (37.84%)		
occurrences (all)	58		
DYSGEUSIA			
subjects affected / exposed	5 / 74 (6.76%)		
occurrences (all)	6		
HEADACHE			
subjects affected / exposed	28 / 74 (37.84%)		
occurrences (all)	40		
HYPOAESTHESIA			
subjects affected / exposed	5 / 74 (6.76%)		
occurrences (all)	6		
NEUROPATHY PERIPHERAL			
subjects affected / exposed	19 / 74 (25.68%)		
occurrences (all)	38		
PARAESTHESIA			
subjects affected / exposed	5 / 74 (6.76%)		
occurrences (all)	7		
PERIPHERAL SENSORY NEUROPATHY			

subjects affected / exposed occurrences (all) SYNCOPE subjects affected / exposed occurrences (all)	31 / 74 (41.89%) 63 4 / 74 (5.41%) 4		
Blood and lymphatic system disorders ANAEMIA subjects affected / exposed occurrences (all) LEUKOCYTOSIS subjects affected / exposed occurrences (all) LEUKOPENIA subjects affected / exposed occurrences (all) NEUTROPENIA subjects affected / exposed occurrences (all) THROMBOCYTOPENIA subjects affected / exposed occurrences (all) THROMBOCYTOSIS subjects affected / exposed occurrences (all)	 27 / 74 (36.49%) 73 7 / 74 (9.46%) 8 9 / 74 (12.16%) 22 17 / 74 (22.97%) 36 28 / 74 (37.84%) 126 4 / 74 (5.41%) 7		
Ear and labyrinth disorders EAR DISCOMFORT subjects affected / exposed occurrences (all)	 4 / 74 (5.41%) 4		
Eye disorders CATARACT subjects affected / exposed occurrences (all) DRY EYE subjects affected / exposed occurrences (all) LACRIMATION INCREASED	 9 / 74 (12.16%) 10 8 / 74 (10.81%) 8		

subjects affected / exposed	4 / 74 (5.41%)		
occurrences (all)	4		
VISION BLURRED			
subjects affected / exposed	7 / 74 (9.46%)		
occurrences (all)	7		
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	23 / 74 (31.08%)		
occurrences (all)	33		
ABDOMINAL PAIN UPPER			
subjects affected / exposed	4 / 74 (5.41%)		
occurrences (all)	4		
CONSTIPATION			
subjects affected / exposed	19 / 74 (25.68%)		
occurrences (all)	23		
DIARRHOEA			
subjects affected / exposed	41 / 74 (55.41%)		
occurrences (all)	59		
DYSPEPSIA			
subjects affected / exposed	8 / 74 (10.81%)		
occurrences (all)	9		
GASTROOESOPHAGEAL REFLUX DISEASE			
subjects affected / exposed	5 / 74 (6.76%)		
occurrences (all)	6		
NAUSEA			
subjects affected / exposed	33 / 74 (44.59%)		
occurrences (all)	65		
VOMITING			
subjects affected / exposed	21 / 74 (28.38%)		
occurrences (all)	28		
Skin and subcutaneous tissue disorders			
ALOPECIA			
subjects affected / exposed	8 / 74 (10.81%)		
occurrences (all)	8		
NIGHT SWEATS			

subjects affected / exposed	10 / 74 (13.51%)		
occurrences (all)	13		
PETECHIAE			
subjects affected / exposed	4 / 74 (5.41%)		
occurrences (all)	8		
PRURITUS			
subjects affected / exposed	10 / 74 (13.51%)		
occurrences (all)	12		
RASH			
subjects affected / exposed	12 / 74 (16.22%)		
occurrences (all)	20		
SKIN LESION			
subjects affected / exposed	4 / 74 (5.41%)		
occurrences (all)	4		
SKIN ULCER			
subjects affected / exposed	4 / 74 (5.41%)		
occurrences (all)	4		
Renal and urinary disorders			
ACUTE KIDNEY INJURY			
subjects affected / exposed	5 / 74 (6.76%)		
occurrences (all)	6		
POLLAKIURIA			
subjects affected / exposed	6 / 74 (8.11%)		
occurrences (all)	6		
PROTEINURIA			
subjects affected / exposed	5 / 74 (6.76%)		
occurrences (all)	6		
URINARY RETENTION			
subjects affected / exposed	4 / 74 (5.41%)		
occurrences (all)	5		
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	21 / 74 (28.38%)		
occurrences (all)	34		
BACK PAIN			

subjects affected / exposed	12 / 74 (16.22%)		
occurrences (all)	22		
BONE PAIN			
subjects affected / exposed	8 / 74 (10.81%)		
occurrences (all)	8		
MUSCLE SPASMS			
subjects affected / exposed	5 / 74 (6.76%)		
occurrences (all)	5		
MUSCULAR WEAKNESS			
subjects affected / exposed	8 / 74 (10.81%)		
occurrences (all)	8		
MUSCULOSKELETAL PAIN			
subjects affected / exposed	5 / 74 (6.76%)		
occurrences (all)	5		
MYALGIA			
subjects affected / exposed	6 / 74 (8.11%)		
occurrences (all)	7		
NECK PAIN			
subjects affected / exposed	4 / 74 (5.41%)		
occurrences (all)	5		
PAIN IN EXTREMITY			
subjects affected / exposed	18 / 74 (24.32%)		
occurrences (all)	31		
Infections and infestations			
BRONCHITIS			
subjects affected / exposed	7 / 74 (9.46%)		
occurrences (all)	7		
HERPES ZOSTER			
subjects affected / exposed	4 / 74 (5.41%)		
occurrences (all)	5		
INFLUENZA			
subjects affected / exposed	8 / 74 (10.81%)		
occurrences (all)	9		
LUNG INFECTION			
subjects affected / exposed	6 / 74 (8.11%)		
occurrences (all)	7		

SINUSITIS			
subjects affected / exposed	14 / 74 (18.92%)		
occurrences (all)	15		
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	14 / 74 (18.92%)		
occurrences (all)	21		
URINARY TRACT INFECTION			
subjects affected / exposed	23 / 74 (31.08%)		
occurrences (all)	40		
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	10 / 74 (13.51%)		
occurrences (all)	11		
DEHYDRATION			
subjects affected / exposed	5 / 74 (6.76%)		
occurrences (all)	5		
HYPERGLYCAEMIA			
subjects affected / exposed	8 / 74 (10.81%)		
occurrences (all)	12		
HYPERKALAEMIA			
subjects affected / exposed	11 / 74 (14.86%)		
occurrences (all)	16		
HYPERURICAEMIA			
subjects affected / exposed	18 / 74 (24.32%)		
occurrences (all)	25		
HYPOCALCAEMIA			
subjects affected / exposed	4 / 74 (5.41%)		
occurrences (all)	4		
HYPOKALAEMIA			
subjects affected / exposed	6 / 74 (8.11%)		
occurrences (all)	6		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 July 2014	• Added ophthalmic examinations • Clarified co-administration of CYP3A4 inhibitors/inducers, breast cancer resistance protein substrates, and organic anion transporting polypeptide inhibitors based on new data • Removed thiocyanate testing as supported by data analysis from Study CCL09101
22 August 2014	• For Cohorts 1 and 2, added an optional twice-daily dosing regimen for subjects who changed to a once-daily dosing regimen after enrolling in this study • Added more thiamine testing time points • Updated safety information
24 July 2015	• Removed Cohort 3 because the parent Study GS-US-354-0101 was closed due to limited efficacy of MMB in the treatment of PV and ET. All subjects enrolled in Cohort 3 were discontinued from treatment and Study GS-US -352-1154 • Added Cohort 4 – subjects who completed 24 weeks on Study GS-US-352-1672
06 November 2017	• Extended protocol study visits to allow continued treatment with MMB as long as the extended access program was available, after which time this study would be terminated

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Cohort 3 was discontinued and excluded from the safety and efficacy analyses.

Data for survival analyses (overall, progression-free, and leukemia-free) could not be presented due to the high level of censoring.

Notes: