Clinical trial results:
A Phase Ib/III, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of vismodegib in combination with ruxolitinib versus placebo and ruxolitinib in patients with intermediate- or high-risk myelofibrosis

Summary

EudraCT number	2015-001620-33
Trial protocol	DE
Global end of trial date	12 July 2017

Results information

Result version number	v1 (current)
This version publication date	20 July 2018
First version publication date	20 July 2018

Trial information

Trial identification

Sponsor protocol code	WO29806

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02593760
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.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	12 July 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	12 July 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The objective of the Phase Ib portion of the study was to assess preliminary safety and efficacy data after the first ten patients completed at least 24 and up to 48 weeks of study treatment (vismodegib plus ruxolitinib).

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 January 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 3
Country: Number of subjects enrolled	Canada: 4
Country: Number of subjects enrolled	Italy: 3
Worldwide total number of subjects	10
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)	3
From 65 to 84 years	7
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

This study was divided into two components. Phase Ib portion of the study consisted of ten participants receiving open-label vismodegib plus ruxolitinib. Phase III portion was planned (with 84 patients in a randomized, placebo-controlled and double-blind manner) but was not conducted.

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	Vismodegib + Ruxolitinib

Arm description:

Participants will receive vismodegib (150 mg PO QD) in combination with ruxolitinib (dose will depend on the participant's baseline platelet count) for up to 48 weeks.

Arm type	Experimental
Investigational medicinal product name	Vismodegib
Investigational medicinal product code	
Other name	Erivedge
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Vismodegib was administered at a dose of 150 mg PO QD for up to 48 weeks.

Investigational medicinal product name	Ruxolitinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Ruxolitinib was administered PO BID at a starting dose depending on the participants's baseline platelet count for up to 48 weeks.

Number of subjects in period 1	Vismodegib + Ruxolitinib
Started	10
Completed	8
Not completed	2
Lack of Efficacy	1
Adverse event, non-fatal	1

Baseline characteristics

Reporting groups	
Reporting group title	Vismodegib + Ruxolitinib
Reporting group description:	
Participants will receive vismodegib (150 mg PO QD) in combination with ruxolitinib (dose will depend on the participant's baseline platelet count) for up to 48 weeks.	

Reporting group values	Vismodegib + Ruxolitinib	Total	
Number of subjects	10	10	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	3	3	
From 65-84 years	7	7	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	66.5		
standard deviation	± 9.4	-	
Gender categorical Units: Subjects			
Female	3	3	
Male	7	7	

End points

End points reporting groups

Reporting group title	Vismodegib + Ruxolitinib

Reporting group description:

Participants will receive vismodegib (150 mg PO QD) in combination with ruxolitinib (dose will depend on the participant's baseline platelet count) for up to 48 weeks.

Primary: Percentage of Participants who Achieve a Greater Than or Equal to (>=) 35% Reduction in Spleen Volume from Baseline at Week 24

End point title	Percentage of Participants who Achieve a Greater Than or Equal to (>=) 35% Reduction in Spleen Volume from Baseline at Week 24[1]

End point description:

Determined by an Independent Review Committee (IRC) Using International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) Revised Response Criteria

End point type	Primary

End point timeframe:

Week 24

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses for this end point.

End point values	Vismodegib + Ruxolitinib			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: percentage of participants				
number (not applicable)	30			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants with Complete Remission (CR) and Partial Remission (PR) at Week 24, as Determined by an IRC Using IWG-MRT Revised Response Criteria

End point title	Percentage of Participants with Complete Remission (CR) and Partial Remission (PR) at Week 24, as Determined by an IRC Using IWG-MRT Revised Response Criteria[2]

End point description:

End point type	Primary

End point timeframe:

Week 24

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses for this end point.

End point values	Vismodegib + Ruxolitinib			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: percentage of participants				
number (not applicable)				
CR	0			
PR	10			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Vismodegib Concentration at Steady State

End point title	Plasma Vismodegib Concentration at Steady State

End point description:

End point type	Secondary

End point timeframe:

Predose (0 hour) on Weeks 6, 12, 24, 36, and 48

End point values	Vismodegib + Ruxolitinib			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: ng/mL				
arithmetic mean (standard deviation)				
Week 6 (n=10)	8530 (± 3340)			
Week 12 (n=9)	10600 (± 4320)			
Week 24 (n=9)	11500 (± 3550)			
Week 36 (n=8)	10800 (± 3830)			
Week 48 (n=8)	10300 (± 2500)			

Statistical analyses

No statistical analyses for this end point

Secondary: Unbound Vismodegib Concentration at Steady State

End point title	Unbound Vismodegib Concentration at Steady State

End point description:

End point type	Secondary

End point timeframe:

Predose (0 hour) on Weeks 6, 12, 24, 36, and 48

End point values	Vismodegib + Ruxolitinib			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: ng/mL				
arithmetic mean (standard deviation)				
Week 6 (n=9)	110 (± 77.2)			
Week 12 (n=9)	112 (± 64.7)			
Week 24 (n=9)	122 (± 63.1)			
Week 36 (n=6)	146 (± 61.3)			
Week 48 (n=5)	135 (± 41.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Alpha 1-Acid Glycoprotein Concentration at Steady State

End point title	Alpha 1-Acid Glycoprotein Concentration at Steady State

End point description:

End point type	Secondary

End point timeframe:

Predose (0 hour) on Weeks 6, 12, 24, 36, and 48

End point values	Vismodegib + Ruxolitinib			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: g/L				
arithmetic mean (standard deviation)				
Week 6 (n=10)	0.994 (± 0.331)			
Week 12 (n=10)	1.17 (± 0.421)			
Week 24 (n=9)	1.21 (± 0.331)			
Week 36 (n=8)	1.06 (± 0.328)			

Week 48 (n=8)	0.997 (± 0.168)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants who Achieve a >= 35% Reduction in Spleen Volume from Baseline, as Determined by an IRC Using IWG-MRT Revised Response Criteria at Week 48

End point title	Percentage of Participants who Achieve a >= 35% Reduction in Spleen Volume from Baseline, as Determined by an IRC Using IWG-MRT Revised Response Criteria at Week 48

End point description:

This outcome measure was specific to Phase III of the study, which was not conducted.

End point type	Secondary

End point timeframe:

Baseline, Week 48

End point values	Vismodegib + Ruxolitinib			
Subject group type	Reporting group			
Number of subjects analysed	0[3]			
Units: percentage of participants				
number (not applicable)				

Notes:

[3] - This outcome measure was specific to Phase III of the study, which was not conducted.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants who Achieve a >= 35% Reduction in Spleen Volume from Baseline, as Determined by an Investigator at Weeks 24 and 48

End point title	Percentage of Participants who Achieve a >= 35% Reduction in Spleen Volume from Baseline, as Determined by an Investigator at Weeks 24 and 48

End point description:

This outcome measure was specific to Phase III of the study, which was not conducted.

End point type	Secondary

End point timeframe:

Baseline, Weeks 24 and 48

End point values	Vismodegib + Ruxolitinib			
Subject group type	Reporting group			
Number of subjects analysed	0[4]			
Units: percentage of participants				
number (not applicable)				

Notes:

[4] - This outcome measure was specific to Phase III of the study, which was not conducted.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with CR and PR, as Determined by an IRC Using IWG-MRT Revised Response Criteria at Week 48

End point title	Percentage of Participants with CR and PR, as Determined by an IRC Using IWG-MRT Revised Response Criteria at Week 48

End point description:

This outcome measure was specific to Phase III of the study, which was not conducted.

End point type	Secondary

End point timeframe:

Week 48

End point values	Vismodegib + Ruxolitinib			
Subject group type	Reporting group			
Number of subjects analysed	0[5]			
Units: percentage of participants				
number (not applicable)				

Notes:

[5] - This outcome measure was specific to Phase III of the study, which was not conducted.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with CR and PR, as Determined by an Investigator at Weeks 24 and 48

End point title	Percentage of Participants with CR and PR, as Determined by an Investigator at Weeks 24 and 48

End point description:

This outcome measure was specific to Phase III of the study, which was not conducted.

End point type	Secondary

End point timeframe:

Weeks 24 and 48

End point values	Vismodegib + Ruxolitinib			
Subject group type	Reporting group			
Number of subjects analysed	0[6]			
Units: percentage of participants				
number (not applicable)				

Notes:

[6] - This outcome measure was specific to Phase III of the study, which was not conducted.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Overall Response Rate (CR, PR, and Clinical Improvement) at Weeks 24 and 48, as Determined by an IRC Using IWG-MRT Revised Response Criteria

End point title	Percentage of Participants with Overall Response Rate (CR, PR, and Clinical Improvement) at Weeks 24 and 48, as Determined by an IRC Using IWG-MRT Revised Response Criteria

End point description:

This outcome measure was specific to Phase III of the study, which was not conducted.

End point type	Secondary

End point timeframe:

Weeks 24 and 48

End point values	Vismodegib + Ruxolitinib			
Subject group type	Reporting group			
Number of subjects analysed	0[7]			
Units: percentage of participants				
number (not applicable)				

Notes:

[7] - This outcome measure was specific to Phase III of the study, which was not conducted.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Overall Response Rate (CR, PR, and Clinical Improvement) at Weeks 24 and 48, as Determined by the Investigator Using IWG-MRT Revised Response Criteria

End point title	Percentage of Participants with Overall Response Rate (CR, PR, and Clinical Improvement) at Weeks 24 and 48, as Determined by the Investigator Using IWG-MRT Revised Response Criteria

End point description:

This outcome measure was specific to Phase III of the study, which was not conducted.

End point type	Secondary

End point timeframe:

Weeks 24 and 48

End point values	Vismodegib + Ruxolitinib			
Subject group type	Reporting group			
Number of subjects analysed	0[8]			
Units: percentage of participants				
number (not applicable)				

Notes:

[8] - This outcome measure was specific to Phase III of the study, which was not conducted.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants who Achieve Anemia Response at Week 24, as Determined by the Investigator Using IWG-MRT Revised Response Criteria

End point title	Percentage of Participants who Achieve Anemia Response at Week 24, as Determined by the Investigator Using IWG-MRT Revised Response Criteria

End point description:

End point type	Secondary

End point timeframe:

Week 24

End point values	Vismodegib + Ruxolitinib			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: percentage of participants				
number (not applicable)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Symptom Response (Participants who Achieve a >= 50% Reduction from Baseline in the Myeloproliferative Neoplasm Symptom Assessment Form [MPN-SAF] Total Symptom Score [TSS])

End point title	Percentage of Participants with Symptom Response (Participants who Achieve a >= 50% Reduction from Baseline in the Myeloproliferative Neoplasm Symptom Assessment Form [MPN-SAF] Total Symptom Score [TSS])

End point description:

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	Vismodegib + Ruxolitinib			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: percentage of participants				
number (not applicable)	71.4			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response, as Determined by the Investigator and an IRC Using IWG-MRT Revised Response Criteria or Death from Any Cause During the Study

End point title	Duration of Response, as Determined by the Investigator and an IRC Using IWG-MRT Revised Response Criteria or Death from Any Cause During the Study

End point description:

This outcome measure was specific to Phase III of the study, which was not conducted.

End point type	Secondary

End point timeframe:

Baseline up to 28 days after the last dose of study drug (52 weeks)

End point values	Vismodegib + Ruxolitinib			
Subject group type	Reporting group			
Number of subjects analysed	0[9]			
Units: N/A				
number (not applicable)				

Notes:

[9] - This outcome measure was specific to Phase III of the study, which was not conducted.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Improvement from Baseline in Bone Marrow Fibrosis at Week 24, as Determined by the Investigator Using the European Consensus Grading System

End point title	Percentage of Participants with Improvement from Baseline in Bone Marrow Fibrosis at Week 24, as Determined by the Investigator Using the European Consensus Grading System

End point description:

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	Vismodegib + Ruxolitinib			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: percentage of participants				
number (not applicable)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Improvement from Baseline in Bone Marrow Fibrosis at Weeks 24 and 48, as Determined by Independent Pathology Review Using the European Consensus Grading System

End point title	Percentage of Participants with Improvement from Baseline in Bone Marrow Fibrosis at Weeks 24 and 48, as Determined by Independent Pathology Review Using the European Consensus Grading System

End point description:

This outcome measure was specific to Phase III of the study, which was not conducted.

End point type	Secondary

End point timeframe:

Baseline, Weeks 24 and 48

End point values	Vismodegib + Ruxolitinib			
Subject group type	Reporting group			
Number of subjects analysed	0[10]			
Units: percentage of participants				
number (not applicable)				

Notes:

[10] - This outcome measure was specific to Phase III of the study, which was not conducted.

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival

End point title	Progression-Free Survival

End point description:

This outcome measure was specific to Phase III of the study, which was not conducted.

End point type	Secondary

End point timeframe:

Baseline up to the end of the study (up to 1 year after completing 48 weeks of treatment by the last participant)

End point values	Vismodegib + Ruxolitinib			
Subject group type	Reporting group			
Number of subjects analysed	0[11]			
Units: N/A				
number (not applicable)				

Notes:

[11] - This outcome measure was specific to Phase III of the study, which was not conducted.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants who Achieve a >= 50% Reduction in Fatigue from Baseline to Weeks 24 and 48 as Measured by MPN-SAF TSS

End point title	Percentage of Participants who Achieve a >= 50% Reduction in Fatigue from Baseline to Weeks 24 and 48 as Measured by MPN-SAF TSS

End point description:

This outcome measure was specific to Phase III of the study, which was not conducted.

End point type	Secondary

End point timeframe:

Baseline, Weeks 24 and 48

End point values	Vismodegib + Ruxolitinib			
Subject group type	Reporting group			
Number of subjects analysed	0[12]			
Units: percentage of participants				
number (not applicable)				

Notes:

[12] - This outcome measure was specific to Phase III of the study, which was not conducted.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants who Achieve a >= 50% Reduction in Other Symptom and Impact Item Scores from Baseline to Weeks 24 and 48, as Measured by the MPN-SAF

End point title	Percentage of Participants who Achieve a >= 50% Reduction in Other Symptom and Impact Item Scores from Baseline to Weeks 24 and 48, as Measured by the MPN-SAF

End point description:

This outcome measure was specific to Phase III of the study, which was not conducted.

End point type	Secondary

End point timeframe:

Baseline, Weeks 24 and 48

End point values	Vismodegib + Ruxolitinib			
Subject group type	Reporting group			
Number of subjects analysed	0[13]			
Units: percentage of participants				
number (not applicable)				

Notes:

[13] - This outcome measure was specific to Phase III of the study, which was not conducted.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants who Achieve a Meaningful Improvement on the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 Scale Scores from Baseline to Weeks 24 and 48

End point title	Percentage of Participants who Achieve a Meaningful Improvement on the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 Scale Scores from Baseline to Weeks 24 and 48

End point description:

Meaningful improvement is defined as a 10-point change. This outcome measure was specific to Phase III of the study, which was not conducted.

End point type	Secondary

End point timeframe:

Baseline, Weeks 24 and 48

End point values	Vismodegib + Ruxolitinib			
Subject group type	Reporting group			
Number of subjects analysed	0[14]			
Units: percentage of participants				
number (not applicable)				

Notes:

[14] - This outcome measure was specific to Phase III of the study, which was not conducted.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

This outcome measure was specific to Phase III of the study, which was not conducted.

End point type	Secondary

End point timeframe:

Baseline up to the end of the study (up to 1 year after completing 48 weeks treatment by the last participant)

End point values	Vismodegib + Ruxolitinib			
Subject group type	Reporting group			
Number of subjects analysed	0[15]			
Units: N/A				
number (not applicable)				

Notes:

[15] - This outcome measure was specific to Phase III of the study, which was not conducted.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Adverse Events (AEs)

End point title	Percentage of Participants with Adverse Events (AEs)

End point description:

End point type	Secondary

End point timeframe:

Baseline up to Month 48

End point values	Vismodegib + Ruxolitinib			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: percentage of participants				
number (not applicable)	100			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with AEs Leading to Treatment Discontinuation or Interruption

End point title	Percentage of Participants with AEs Leading to Treatment Discontinuation or Interruption

End point description:

End point type	Secondary

End point timeframe:

Baseline up to Month 48

End point values	Vismodegib + Ruxolitinib			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: percentage of participants				
number (not applicable)				
Treatment Discontinutation	10			
Vismodegib Interruption	40			
Ruxolitinib Interruption	20			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Grade 3, 4 or 5 AEs

End point title	Percentage of Participants with Grade 3, 4 or 5 AEs

End point description:

AEs were graded according to NCI CTCAE v4.0. Grade 3 includes events that are severe or medically significant, but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living. Grade 4 include events that have life-threatening consequences or urgent intervention indicated. Grade 5 AEs are those events which led to death..

End point type	Secondary

End point timeframe:

Baseline up to 48 months.

End point values	Vismodegib + Ruxolitinib			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: percentage of participants				
number (not applicable)				
Grade 3	40			
Grade 4	30			
Grade 5	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 48 months from baseline until clinical cutoff of 30-Oct-2017.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Vismodegib + Ruxolitinib

Reporting group description:

Participants will receive vismodegib (150 mg PO QD) in combination with ruxolitinib (dose will depend on the participant's baseline platelet count) for up to 48 weeks.

Serious adverse events	Vismodegib + Ruxolitinib		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 10 (30.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Lung infiltration			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Enterocolitis infectious			

subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Vismodegib + Ruxolitinib		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 10 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Haemangioma of skin			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Malignant melanoma			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Prostate cancer			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Hypertension			

subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	2		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	2		
Pain			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	2		
Dyspnoea exertional			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Epistaxis			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	2		
Oropharyngeal pain			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	2		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Platelet count decreased			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		

Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Fall			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	2		
Injury			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Tendon Rupture			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Extrasystoles			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Dysgeusia			
subjects affected / exposed	5 / 10 (50.00%)		
occurrences (all)	5		
Headache			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Neuropathy peripheral			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	2		
Leukocytosis			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Neutropenia			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	6		
Thrombocytopenia			
subjects affected / exposed	5 / 10 (50.00%)		
occurrences (all)	6		
Eye disorders			
Vision Blurred			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Dry eye			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 10 (30.00%)		
occurrences (all)	4		
Diarrhoea			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Duodenal stenosis			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Epigastric Discomfort			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	4 / 10 (40.00%)		
occurrences (all)	5		
Oral mucosal erythema			

subjects affected / exposed occurrences (all) Tongue ulceration subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1 1 / 10 (10.00%) 1 1 / 10 (10.00%) 2		
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all) Hair growth abnormal subjects affected / exposed occurrences (all) Hyperkeratosis subjects affected / exposed occurrences (all) Pruritus subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all) Seborrhoea subjects affected / exposed occurrences (all)	 7 / 10 (70.00%) 7 1 / 10 (10.00%) 1 1 / 10 (10.00%) 1 1 / 10 (10.00%) 1 1 / 10 (10.00%) 1 1 / 10 (10.00%) 1		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Arthritis subjects affected / exposed occurrences (all) Coccydynia	 1 / 10 (10.00%) 1 1 / 10 (10.00%) 1		

subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Muscle Spasms			
subjects affected / exposed	10 / 10 (100.00%)		
occurrences (all)	14		
Pain in Extremity			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Clostridium difficile infection			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	6		
Diverticulitis			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Folliculitis			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Rash Pustular			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Upper respiratory infection			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Fluid Overload			

subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Gout			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Hyperuricaemia			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 May 2016	Key changes to the protocol included assessment of data at Week 24 for the Phase Ib portion of the study prior to initiation of the Phase III portion and, clarifications of the outcome measures used in Phase Ib.
10 May 2017	Key change to the protocol was to the inclusion criteria in the contraception and blood donation times from 9 or 24 months to 24 months.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported