Clinical trial results:
A Phase II Trial to Evaluate the Activity of Imetelstat (GRN163L) in Patients with Essential Thrombocythemia or Polycythemia Vera who Require Cytoreduction and Have Failed or Are Intolerant to Previous Therapy, or who Refuse Standard Therapy

Summary

EudraCT number	2010-023076-10
Trial protocol	DE
Global end of trial date	06 January 2015

Results information

Result version number	v1 (current)
This version publication date	26 June 2016
First version publication date	26 June 2016

Trial information

Trial identification

Sponsor protocol code	CP14B015

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01243073
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Geron Corporation
Sponsor organisation address	149 Commonwealth Drive, Menlo Park, United States, 94025
Public contact	Anna Krassowska, Geron Corporation, 1 650-473-7700, media@geron.com
Scientific contact	Bart Burington, Geron Corporation, 1 650-473-7700, info@geron.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	06 April 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 January 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

For patients with ET: To obtain a preliminary estimate of efficacy of imetelstat, as measured by best hematologic response within the first year of therapy in patients with ET who have failed or are intolerant to at least one prior therapy, or who have refused standard therapy.

For patients with PV, to be enrolled exclusively in the U.S. and Switzerland: To obtain a preliminary estimate of efficacy of imetelstat, as measured by maintenance of Hct < 45% in men and < 42% in women (or pre-specified Hct count that is tolerable) without phlebotomy or myelosuppressive therapy beginning within the first year of therapy in patients with PV who have failed or are intolerant to at least one prior therapy, or who have refused standard therapy.

Protection of trial subjects:

A safety committee internal to Geron will review the safety data after approximately every 3 months or after every 5 patients have received their first imetelstat infusion, whichever is earlier. The committee may adjust the timing of the review from the defined schedule, depending on the rate of enrollment. The tolerability of the 9.4 mg/kg dose will be assessed on an ongoing basis as part of this safety review. After completion of enrollment, the internal safety committee will review the safety data approximately every 3 months until all patients have terminated from the study. The safety review committee will consist of a clinician (Medical Monitor), Drug Safety Scientist, and a biostatistician. The findings of the safety committee will be shared with study Investigators. The Medical Monitor or Drug Safety Scientist may convene a meeting sooner should any concerns arise from review of data or from the Investigators. Additionally, a futility analysis is planned after 10 ET patients have been treated for 4 months, or have discontinued study prior to completing 4 months of treatment.
As introduced in amendment 4, the study will include extended hepatic safety follow-up for all patients in the study who have liver biochemistry abnormalities or hepatic adverse events that first appeared during imetelstat treatment, or worsened from baseline during treatment, and were continuing at the time the patient stopped imetelstat treatment. Liver biochemistries (alkaline phosphatase [ALP], aspartate aminotransferase [AST], alanine aminotransferase [ALT], and bilirubin), renal function tests, adverse events, and concomitant medications will be collected approximately once monthly until the liver biochemistry abnormalities and/or hepatic adverse events have resolved to normal or baseline, or in the event resolution does not occur, for up to 6 months after the treatment termination visit of imetelstat.

Background therapy:

Premedication for Infusions: All patients will require premedication with diphenhydramine (25-50 mg, PO or IV) and dexamethasone (10-20 mg PO or IV) or equivalent before receiving imetelstat.

Evidence for comparator:

There were no comparator treatments in this study.

Actual start date of recruitment	14 January 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	Switzerland: 3
Country: Number of subjects enrolled	United States: 14
Worldwide total number of subjects	20
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)	14
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Twenty-one patients were enrolled in the United States, Germany and Switzerland, and 20 patients (95.2%) were treated, including 18 with ET
and 2 with PV. One enrolled patient was found ineligible during screening and did not receive any treatment.

Pre-assignment

Screening details:

Screening criteria included adult males and females with ET or PV, ECOG status of 0–2, INR/PT and aPTT < 1.5 x ULN, serum creatinine <= 2 mg/dL, serum bilirubin < 2, AST (SGOT) and ALT (SGPT) <= 2.5 x ULN, and ALP < 2.5 x ULN. ET patients had platelets > 600k/µL, ANC >= 1500/µL and Hgb >= 10 g/dL and were failed/intolerant to >= 1 prior therapy.

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Essential Thrombocythemia (ET)

Arm description:

Patients with Essential Thrombocythemia (ET)

Arm type	Experimental
Investigational medicinal product name	Imetelstat sodium
Investigational medicinal product code	JNJ-63935937
Other name	Imetelstat, GRN163L
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Imetelstat 7.5 mg/kg (prior to Amendment 1) or 9.4 mg/kg (subsequent to Amendment 1) was administered as a weekly 2-hour IV infusion (± 10 minutes) in the induction phase, followed by a maintenance phase of intermittent dosing using the same administration rate of 2 hours (± 10 minutes). The baseline weight was used to calculate the dose of imetelstat. The dose was recalculated if there was a ≥ 10% weight change from baseline. Patients had their imetelstat dose and schedule modified based on: 1) attainment of target platelet count (ET) or hematocrit with phlebotomy independence (PV) (hematologic response), 2) hematologic toxicity, and 3) non-hematologic toxicity. Dose escalation up to 11.7 mg/kg was allowed. A cycle was considered to be 28 days for laboratory and correlative PD sample collection purposes. Dosing in the maintenance phase was based on platelet levels and tolerability; therefore, a dose may or may not have been administered in a given cycle.

Arm title	Polycythemia Vera (PV)

Arm description:

Patients with Polycythemia Vera (PV)

Arm type	Experimental
Investigational medicinal product name	Imetelstat sodium
Investigational medicinal product code	JNJ-63935937
Other name	Imetelstat, GRN163L
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Imetelstat 7.5 mg/kg (prior to Amendment 1) or 9.4 mg/kg (subsequent to Amendment 1) was administered as a weekly 2-hour IV infusion (± 10 minutes) in the induction phase, followed by a

maintenance phase of intermittent dosing using the same administration rate of 2 hours (± 10 minutes). The baseline weight was used to calculate the dose of imetelstat. The dose was recalculated if there was a ≥ 10% weight change from baseline. Patients had their imetelstat dose and schedule modified based on: 1) attainment of target platelet count (ET) or hematocrit with phlebotomy independence (PV) (hematologic response), 2) hematologic toxicity, and 3) non-hematologic toxicity. Dose escalation up to 11.7 mg/kg was allowed. A cycle was considered to be 28 days for laboratory and correlative PD sample collection purposes. Dosing in the maintenance phase was based on platelet levels and tolerability; therefore, a dose may or may not have been administered in a given cycle.

Number of subjects in period 1	Essential Thrombocythemia (ET)	Polycythemia Vera (PV)
Started	18	2
Completed	18	2

Period 2

Period 2 title	Final Analysis
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Essential Thrombocythemia (ET)

Arm description:

Patients with Essential Thrombocythemia (ET)

Arm type	Experimental
Investigational medicinal product name	Imetelstat sodium
Investigational medicinal product code	JNJ-63935937
Other name	Imetelstat, GRN163L
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Imetelstat 7.5 mg/kg (prior to Amendment 1) or 9.4 mg/kg (subsequent to Amendment 1) was administered as a weekly 2-hour IV infusion (± 10 minutes) in the induction phase, followed by a maintenance phase of intermittent dosing using the same administration rate of 2 hours (± 10 minutes). The baseline weight was used to calculate the dose of imetelstat. The dose was recalculated if there was a ≥ 10% weight change from baseline. Patients had their imetelstat dose and schedule modified based on: 1) attainment of target platelet count (ET) or hematocrit with phlebotomy independence (PV) (hematologic response), 2) hematologic toxicity, and 3) non-hematologic toxicity. Dose escalation up to 11.7 mg/kg was allowed. A cycle was considered to be 28 days for laboratory and correlative PD sample collection purposes. Dosing in the maintenance phase was based on platelet levels and tolerability; therefore, a dose may or may not have been administered in a given cycle.

Arm title	Polycythemia Vera (PV)

Arm description:

Patients with Polycythemia Vera (PV)

Arm type	Experimental

Investigational medicinal product name	Imetelstat sodium
Investigational medicinal product code	JNJ-63935937
Other name	Imetelstat, GRN163L
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Imetelstat 7.5 mg/kg (prior to Amendment 1) or 9.4 mg/kg (subsequent to Amendment 1) was administered as a weekly 2-hour IV infusion (± 10 minutes) in the induction phase, followed by a maintenance phase of intermittent dosing using the same administration rate of 2 hours (± 10 minutes). The baseline weight was used to calculate the dose of imetelstat. The dose was recalculated if there was a ≥ 10% weight change from baseline. Patients had their imetelstat dose and schedule modified based on: 1) attainment of target platelet count (ET) or hematocrit with phlebotomy independence (PV) (hematologic response), 2) hematologic toxicity, and 3) non-hematologic toxicity. Dose escalation up to 11.7 mg/kg was allowed. A cycle was considered to be 28 days for laboratory and correlative PD sample collection purposes. Dosing in the maintenance phase was based on platelet levels and tolerability; therefore, a dose may or may not have been administered in a given cycle.

Number of subjects in period 2	Essential Thrombocythemia (ET)	Polycythemia Vera (PV)
Started	18	2
Completed	18	2

Baseline characteristics

Reporting groups	
Reporting group title	Essential Thrombocythemia (ET)
Reporting group description: Patients with Essential Thrombocythemia (ET)	
Reporting group title	Polycythemia Vera (PV)
Reporting group description: Patients with Polycythemia Vera (PV)	

Reporting group values	Essential Thrombocythemia (ET)	Polycythemia Vera (PV)	Total
Number of subjects	18	2	20
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	12	2	14
From 65-84 years	6	0	6
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	10	1	11
Male	8	1	9
History of thrombosis			
History of thrombosis			
Units: Subjects			
Yes	5	1	6
No	13	1	14
Splenomegaly			
Splenomegaly >= 5cm below left costal margin by palpation			
Units: Subjects			
Yes	1	0	1
No	17	2	19
Bone marrow reticulin fibrosis grade 1+ or 2+			
Bone marrow reticulin fibrosis grade 1+ or 2+			
Units: Subjects			
Yes	7	2	9
No	11	0	11
Bone marrow megakaryocyte hyperplasia			
Bone marrow megakaryocyte hyperplasia			
Units: Subjects			

Yes	15	1	16
No	3	1	4
Previous treatment: hydroxyurea			
Previous treatment with hydroxyurea			
Units: Subjects			
Yes	17	1	18
No	1	1	2
Previous treatment: anagrelide			
Previous treatment with anagrelide			
Units: Subjects			
Yes	13	0	13
No	5	2	7
Previous treatment: interferon			
Previous treatment with interferon			
Units: Subjects			
Yes	4	2	6
No	14	0	14
Resistant to >= 1 prior therapy			
Resistant to one or more prior therapies for ET or PV			
Units: Subjects			
Yes	9	0	9
No	9	2	11
Unacceptable side effects from >= 1 prior therapy			
Unacceptable side effects from one or more prior therapies for ET or PV			
Units: Subjects			
Yes	14	1	15
No	4	1	5
Mutation: JAK2 V617F			
Janus kinase 2 mutant allele burden at baseline			
Units: Subjects			
Yes	9	2	11
No	9	0	9
Mutation: MPL W515L or MPL W515K			
Myeloproliferative leukemia virus oncogene homology (MPL) mutant allele burden detected at baseline			
Units: Subjects			
Yes	2	0	2
No	16	2	18
Mutation: CALR			
Calreticulin mutant allele burden detected at baseline			
Units: Subjects			
Yes	5	0	5
No	13	2	15
Years since initial diagnosis			
Years since initial diagnosis			
Units: Years			
median	7.2	12	
full range (min-max)	0.3 to 24.9	11.6 to 12.5	-
Platelet count			
Platelet count			
Units: per mm3			

median	787.5	216	
full range (min-max)	521 to 1359	152 to 280	-
Prior therapy: number of prior therapies			
Number of prior therapies for ET or PV			
Units: Integer			
median	2	1.5	
full range (min-max)	1 to 4	1 to 2	-
Hemoglobin			
Hemoglobin			
Units: g/dL			
median	12.3	13.5	
full range (min-max)	8.7 to 15.1	13.5 to 13.5	-

End points

End points reporting groups

Reporting group title	Essential Thrombocythemia (ET)
Reporting group description: Patients with Essential Thrombocythemia (ET)	
Reporting group title	Polycythemia Vera (PV)
Reporting group description: Patients with Polycythemia Vera (PV)	
Reporting group title	Essential Thrombocythemia (ET)
Reporting group description: Patients with Essential Thrombocythemia (ET)	
Reporting group title	Polycythemia Vera (PV)
Reporting group description: Patients with Polycythemia Vera (PV)	

Primary: Overall response

End point title	Overall response[1]

End point description:

Efficacy will be determined by best overall hematologic response rate beginning within the first year of imetelstat therapy, defined as follows:
• ET
− CR = Normalization of platelets (≤ 400 x 103/µL), maintained for at least 4 consecutive weeks, in the absence of new thromboembolic events
− PR = platelets ≤ 600 x 103/µL OR a 50% reduction in platelet counts (but > 400 x 103/µL), maintained for at least 4 consecutive weeks, in the absence of new thromboembolic events
• PV
− Hematocrit < 45% in men and < 42% in women (or pre-specified Hct count that is tolerable) with independence from other PV-related therapies including phlebotomy, which is maintained in response to imetelstat therapy for ≥ 4 months, and in the absence of new thromboembolic events.

End point type	Primary

End point timeframe:

Efficacy will be determined by best overall hematologic response rate beginning within the first year of imetelstat therapy

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: This single-arm study has two cohorts for different diseases, but no comparator arm. Comparative statistical analyses therefore do not apply, while single-arm analyses, such as a confidence interval (CI) for a single-arm response rate, currently result in validation errors. The impact of omitting statistical analyses for this study is minimal, since, for the two cohorts, the End point values page contains complete data on the primary endpoint so that researchers can compute CIs independently.

End point values	Essential Thrombocythemia (ET)	Polycythemia Vera (PV)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	2		
Units: Integer				
Response	18	2		
Non-response	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Hematologic complete and partial response

End point title	Hematologic complete and partial response

End point description:

Full response category breakout for primary endpoint of hematologic response. Refer to Overall Response for the primary analysis of the primary endpoint.
Efficacy will be determined by best overall hematologic response rate beginning within the first year of imetelstat therapy, defined as follows:
• ET
− CR = Normalization of platelets (≤ 400 x 103/µL), maintained for at least 4 consecutive weeks, in the absence of new thromboembolic events
− PR = platelets ≤ 600 x 103/µL OR a 50% reduction in platelet counts (but > 400 x 103/µL), maintained for at least 4 consecutive weeks, in the absence of new thromboembolic events
• PV
− Hematocrit < 45% in men and < 42% in women (or pre-specified Hct count that is tolerable) with independence from other PV-related therapies including phlebotomy, which is maintained in response to imetelstat therapy for ≥ 4 months, and in the absence of new thromboembolic events.

End point type	Secondary

End point timeframe:

Final analysis including all follow-up for ET and PV patients.

End point values	Essential Thrombocythemia (ET)	Polycythemia Vera (PV)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	2		
Units: Integer				
Complete response	16	0		
Partial response	2	0		
Non-response	0	0		
Hematologic response	0	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of hematologic response

End point title	Duration of hematologic response

End point description:

For patients who achieve hematologic responses, duration of hematologic response is defined as the time from the first hematologic assessment to the time of confirmed hematologic disease progression

(loss of response for 2 cycles despite maximal dose of 11.7 mg/kg/week), occurrence of thromboembolic events, or death due to any cause, whichever occurs first. Fluctuations between responder and non-responder status (ET and PV) are allowed, provided that the patient continues to respond to ongoing treatment. Patients who are lost to follow-up, discontinue study, or initiate other ET- or PV-directed therapy before documented disease progression will be censored at the last assessment when patients are progression-free. Duration of hematologic response will be estimated using the Kaplan-Meier method. Approximate 95% confidence intervals for median duration of hematologic response will be computed using the formula proposed by Brookmeyer and Crowley.

End point type	Secondary

End point timeframe:

Final analysis including all follow-up for ET patients with hematologic response. Estimates are not available for PV due to the small sample size of 2.

End point values	Essential Thrombocythemia (ET)			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: Months				
number (confidence interval 95%)	29.5 (10.9 to 99999999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Molecular response

End point title	Molecular response

End point description:

Molecular response rate is the percentage of patients who achieve a CR or a PR as defined below:
Molecular CR
Reduction of any specific molecular abnormality to undetectable levels
Molecular PR
1) A reduction of ≥ 50% from baseline value in patients with < 50% mutant allele burden at baseline, OR
2) A reduction of ≥ 25% from baseline value in patients with > 50% mutant allele burden at baseline.
1 Applies only to patients with a baseline value of mutant allele burden ≥ 10%. Allele burden is defined as percent mutant allele over total alleles in granulocytes.
The molecular response analysis was performed only in patients with JAK2, CALR or MPL mutations at baseline.

End point type	Secondary

End point timeframe:

Final analysis with all follow-up on patients with driver mutation allelic burdens at baseline

End point values	Essential Thrombocythemia (ET)	Polycythemia Vera (PV)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16[2]	1[3]		
Units: Integer				
Response	10	0		
Non-response	6	1		

Notes:

[2] - 2 patients had no detectable driver mutation allele burden at baseline

[3] - One PV patient had no detectable JAK2 V617F mutant allele burden at baseline.

Statistical analyses

No statistical analyses for this end point

Secondary: Clinicohematologic response

End point title	Clinicohematologic response

End point description:

ET
CR
1) Platelet count ≤ 400 x 103/µL, AND
2) No disease related symptoms, AND
3) Normal spleen size1, AND
4) WBC ≤ 10 x 103/µL

PR
In patients who do not fulfill the criteria for CR, Platelet count ≤ 600 x 103/µL or decrease > 50% from baseline
No Response
Any response that does not satisfy complete or partial response

PV
CR
1) Hematocrit < 45% for males or < 42% for females without phlebotomy AND
2) Platelet count ≤ 400 x 103/µL, AND
3) No disease related symptoms, AND
4) Normal spleen size1, AND
5) WBC ≤ 10 x 103/µL

PR
In patients who do not fulfill the criteria for CR, hematocrit < 45% without phlebotomy OR response in 3 or more of the other criteria

No Response
Any response that does not satisfy complete or partial response

End point type	Secondary

End point timeframe:

Final analysis with all follow-up on ET and PV patients.

End point values	Essential Thrombocythemia (ET)	Polycythemia Vera (PV)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	2		
Units: Integer				
Response	18	2		
Non-response	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: BM histologic response

End point title	BM histologic response

End point description:

Disappearance of megakaryocyte hyperplasia in bone marrow. The analysis of BM histologic response will include only those patients with an abnormal baseline BM sample and at least one evaluable post-baseline sample.

End point type	Secondary

End point timeframe:

Final analysis including all follow-up for ET patients with hematologic response. Estimates are not available for PV due to the small sample size of 2 and insufficient bone marrow samples.

End point values	Essential Thrombocythemia (ET)			
Subject group type	Reporting group			
Number of subjects analysed	14[4]			
Units: Integer				
Response	2			
Non-response	12			

Notes:

[4] - Fourteen patients had baseline megakaryocyte hyperplasia and at least one post-baseline assessment

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Final analysis including all follow-up for ET and PV patients

Adverse event reporting additional description:

The safety and tolerability of imetelstat was assessed by the frequency, severity, and nature of adverse events, laboratory abnormalities, and vital signs. All patients who received any amount of imetelstat were included.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13.0

Reporting groups

Reporting group title	Treated patients

Reporting group description:

All treated patients

Serious adverse events	Treated patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 20 (55.00%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Femoral neck fracture			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pelvic fracture			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rib fracture			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac failure			

subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatic encephalopathy			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Presyncope			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Infusion related reaction			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastric ulcer			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Oesophageal varices haemorrhage			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Small intestinal obstruction			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Myalgia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Osteitis			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Osteomyelitis			

subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Septic shock			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin graft infection			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Upper respiratory tract infection			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Wound infection			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Treated patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 20 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Vascular disorders			
Flushing			
subjects affected / exposed	4 / 20 (20.00%)		
occurrences (all)	6		
Hypertension			

subjects affected / exposed	4 / 20 (20.00%)		
occurrences (all)	4		
Orthostatic hypotension			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Phlebitis			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	11		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	3		
Chest pain			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	3		
Chills			
subjects affected / exposed	8 / 20 (40.00%)		
occurrences (all)	11		
Diarrhoea			
subjects affected / exposed	14 / 20 (70.00%)		
occurrences (all)	30		
Fatigue			
subjects affected / exposed	18 / 20 (90.00%)		
occurrences (all)	45		
Influenza like illness			
subjects affected / exposed	5 / 20 (25.00%)		
occurrences (all)	7		
Infusion site phlebitis			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Malaise			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Mouth ulceration			

subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	4		
Non-cardiac chest pain			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	3		
Oedema			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	3		
Oedema peripheral			
subjects affected / exposed	9 / 20 (45.00%)		
occurrences (all)	15		
Pain			
subjects affected / exposed	4 / 20 (20.00%)		
occurrences (all)	7		
Pyrexia			
subjects affected / exposed	10 / 20 (50.00%)		
occurrences (all)	18		
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Vaginal haemorrhage			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	3		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	9 / 20 (45.00%)		
occurrences (all)	11		
Dyspnoea			
subjects affected / exposed	5 / 20 (25.00%)		
occurrences (all)	8		
Dyspnoea exertional			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	10		
Epistaxis			

subjects affected / exposed	11 / 20 (55.00%)		
occurrences (all)	24		
Nasal congestion			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	3		
Oropharyngeal pain			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	3		
Rhinitis allergic			
subjects affected / exposed	5 / 20 (25.00%)		
occurrences (all)	5		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	3		
Confusional state			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	3		
Depression			
subjects affected / exposed	4 / 20 (20.00%)		
occurrences (all)	4		
Insomnia			
subjects affected / exposed	8 / 20 (40.00%)		
occurrences (all)	8		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	10 / 20 (50.00%)		
occurrences (all)	26		
Aspartate aminotransferase increased			
subjects affected / exposed	10 / 20 (50.00%)		
occurrences (all)	26		
Blood alkaline phosphatase increased			
subjects affected / exposed	5 / 20 (25.00%)		
occurrences (all)	16		
Blood bilirubin increased			

subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Blood creatinine increased			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	4		
Lipase increased			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	5		
Neutrophil count decreased			
subjects affected / exposed	7 / 20 (35.00%)		
occurrences (all)	32		
Platelet count decreased			
subjects affected / exposed	4 / 20 (20.00%)		
occurrences (all)	6		
Weight decreased			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
White blood cell count decreased			
subjects affected / exposed	6 / 20 (30.00%)		
occurrences (all)	24		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	7 / 20 (35.00%)		
occurrences (all)	7		
Fall			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Procedural pain			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	4		
Traumatic haemorrhage			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Nervous system disorders			

Amnesia				
subjects affected / exposed	3 / 20 (15.00%)			
occurrences (all)	3			
Balance disorder				
subjects affected / exposed	2 / 20 (10.00%)			
occurrences (all)	2			
Dizziness				
subjects affected / exposed	13 / 20 (65.00%)			
occurrences (all)	19			
Dysgeusia				
subjects affected / exposed	7 / 20 (35.00%)			
occurrences (all)	13			
Headache				
subjects affected / exposed	10 / 20 (50.00%)			
occurrences (all)	36			
Hypoaesthesia				
subjects affected / exposed	3 / 20 (15.00%)			
occurrences (all)	4			
Memory impairment				
subjects affected / exposed	2 / 20 (10.00%)			
occurrences (all)	2			
Migraine				
subjects affected / exposed	2 / 20 (10.00%)			
occurrences (all)	2			
Neuropathy peripheral				
subjects affected / exposed	3 / 20 (15.00%)			
occurrences (all)	3			
Paraesthesia				
subjects affected / exposed	2 / 20 (10.00%)			
occurrences (all)	4			
Peripheral sensory neuropathy				
subjects affected / exposed	2 / 20 (10.00%)			
occurrences (all)	3			
Presyncope				
subjects affected / exposed	2 / 20 (10.00%)			
occurrences (all)	2			

Sciatica subjects affected / exposed occurrences (all)	3 / 20 (15.00%) 3		
Syncope subjects affected / exposed occurrences (all)	2 / 20 (10.00%) 2		
Tremor subjects affected / exposed occurrences (all)	5 / 20 (25.00%) 8		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	9 / 20 (45.00%) 22		
Neutropenia subjects affected / exposed occurrences (all)	6 / 20 (30.00%) 12		
Thrombocytopenia subjects affected / exposed occurrences (all)	3 / 20 (15.00%) 4		
Ear and labyrinth disorders Deafness subjects affected / exposed occurrences (all)	2 / 20 (10.00%) 2		
Vertigo subjects affected / exposed occurrences (all)	2 / 20 (10.00%) 2		
Eye disorders Cataract subjects affected / exposed occurrences (all)	2 / 20 (10.00%) 2		
Vision blurred subjects affected / exposed occurrences (all)	4 / 20 (20.00%) 29		
Gastrointestinal disorders Abdominal discomfort subjects affected / exposed occurrences (all)	2 / 20 (10.00%) 2		

Abdominal distension				
subjects affected / exposed	3 / 20 (15.00%)			
occurrences (all)	6			
Abdominal pain				
subjects affected / exposed	4 / 20 (20.00%)			
occurrences (all)	4			
Abdominal pain upper				
subjects affected / exposed	4 / 20 (20.00%)			
occurrences (all)	5			
Constipation				
subjects affected / exposed	9 / 20 (45.00%)			
occurrences (all)	14			
Dry mouth				
subjects affected / exposed	2 / 20 (10.00%)			
occurrences (all)	2			
Dyspepsia				
subjects affected / exposed	5 / 20 (25.00%)			
occurrences (all)	6			
Flatulence				
subjects affected / exposed	3 / 20 (15.00%)			
occurrences (all)	4			
Gastrooesophageal reflux disease				
subjects affected / exposed	4 / 20 (20.00%)			
occurrences (all)	4			
Gingival bleeding				
subjects affected / exposed	5 / 20 (25.00%)			
occurrences (all)	5			
Nausea				
subjects affected / exposed	15 / 20 (75.00%)			
occurrences (all)	33			
Pancreatitis				
subjects affected / exposed	2 / 20 (10.00%)			
occurrences (all)	2			
Rectal haemorrhage				
subjects affected / exposed	2 / 20 (10.00%)			
occurrences (all)	2			

Stomatitis			
subjects affected / exposed	5 / 20 (25.00%)		
occurrences (all)	5		
Toothache			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Vomiting			
subjects affected / exposed	7 / 20 (35.00%)		
occurrences (all)	7		
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	4 / 20 (20.00%)		
occurrences (all)	4		
Eczema			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	3		
Night sweats			
subjects affected / exposed	5 / 20 (25.00%)		
occurrences (all)	6		
Pruritus			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Rash			
subjects affected / exposed	6 / 20 (30.00%)		
occurrences (all)	11		
Rash maculo-papular			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Scab			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Skin hyperpigmentation			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	3		
Skin lesion			

subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Urticaria			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	3		
Renal and urinary disorders			
Cystitis noninfective			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	3		
Micturition urgency			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	3		
Endocrine disorders			
Hypogonadism			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	9 / 20 (45.00%)		
occurrences (all)	14		
Back pain			
subjects affected / exposed	6 / 20 (30.00%)		
occurrences (all)	12		
Bone pain			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	4		
Flank pain			
subjects affected / exposed	4 / 20 (20.00%)		
occurrences (all)	4		
Muscle spasms			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	4		
Muscular weakness			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	3		
Musculoskeletal pain			

subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	3		
Myalgia			
subjects affected / exposed	4 / 20 (20.00%)		
occurrences (all)	5		
Pain in extremity			
subjects affected / exposed	7 / 20 (35.00%)		
occurrences (all)	10		
Synovial cyst			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Infections and infestations			
Influenza			
subjects affected / exposed	4 / 20 (20.00%)		
occurrences (all)	9		
Nasopharyngitis			
subjects affected / exposed	4 / 20 (20.00%)		
occurrences (all)	8		
Rash pustular			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	3		
Sinusitis			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	3		
Upper respiratory tract infection			
subjects affected / exposed	7 / 20 (35.00%)		
occurrences (all)	10		
Urinary tract infection			
subjects affected / exposed	4 / 20 (20.00%)		
occurrences (all)	4		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	9 / 20 (45.00%)		
occurrences (all)	11		
Hyperglycaemia			

subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	4		
Hyperuricaemia			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	3		
Hypoalbuminaemia			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Hypokalaemia			
subjects affected / exposed	6 / 20 (30.00%)		
occurrences (all)	15		
Iron deficiency			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 September 2011	1. The requirement for a 4-week washout period from the last dose of the patient's current therapy until start of imetelstat administration has been removed. 2. An induction phase and a maintenance phase of imetelstat treatment has been defined. The goal of weekly induction treatment is to obtain rapid disease control to reduce the likelihood of clinical sequelae from a prolonged thrombocythemic state. Following this, a maintenance phase will be initiated that may allow less intensive dosing while maintaining the hematologic response (i.e. dosing at approximately every 4 weeks, titrated to platelet levels). 3. A change has been made to the timing of safety reviews by the internal safety committee. In the original protocol, reviews occurred after every 10 patients. Review of safety data will now occur every 3 months or after every 5 patients have been treated, whichever is earlier.
30 March 2012	1. The study population has been expanded to include patients with polycythemia vera (PV). PV patients are to be enrolled exclusively in the U.S. and Switzerland. 2. As the half-life of red blood cells is significantly longer than that of platelets, it is possible that the effects of inhibition of the neoplastic progenitor cell in the hematocrit (Hct) will not be observed as quickly in patients with PV compared with platelet counts in patients with ET. Thus, additional safety measures have been implemented in this study, including allowing phlebotomy as needed during the induction phase. In the maintenance phase, phlebotomy should only be used if repeat imetelstat dosing (including either increased dosing or frequency) is not sufficient in reducing Hct levels. 3. To obtain additional safety and efficacy data associated with extended treatment of imetelstat, continued administration of imetelstat will now be allowed for up to 2 additional years for those patients who are deriving benefit (defined as partial hematologic response or better and/or improvement of clinical symptoms per investigator assessment) at the end of 1 year of treatment.

02 July 2013	1. Following the most recent Internal Safety Monitoring Committee review on 31 Jan 2013, an emerging safety signal was identified in this trial. Abnormalities in serum aminotransferases (aspartate aminotransferase [AST], alanine aminotransferase [ALT]), alkaline phosphatase and/or bilirubin were observed in all 16 treated patients. As a result of these observations, the Sponsor communicated these findings to investigators, ethics committees, and regulatory agencies for all imetelstat trials with active patients in March 2013. To further understand and mitigate this potential risk, Geron has conducted an internal investigation of the safety signal by reviewing data from all imetelstat clinical trials across indications, informed and obtained feedback from the FDA, and consulted with external hepatologists. No progressive worsening of hepatic biochemistry elevations or clinical sequelae has been observed at this point. However as precaution, Geron is amending the protocol to add dose modification and trial termination guidance for observed hepatobiliary adverse events and liver investigations. Additional required monitoring of abnormal liver biochemistries and further tests, such as obtaining a viral hepatitis panel, are also included in this amendment. 2. Sponsor has reprioritized the imetelstat development program and will discontinue further exploratory biomarker analysis in this trial. This includes the collection and analysis of colony-forming unit-megakaryocytes (CFU-Mk), colonyforming unit-erythrocytes (CFU-E), telomerase activity, and telomere length. Janus kinase 2 (JAK2)/myeloproliferative leukemia (MPL) mutation and allele burden assessment will continue per protocol. 3. The study has already achieved proof-of-concept for imetelstat in essential thrombocythemia (ET) based on 20 treated patients (18 ET and 2 polycythemia vera [PV]) and will be closed to enrollment as of the end of December 2012.
24 March 2014	This amendment will provide for continued safety surveillance as part of an extended hepatic safety follow-up period of all patients in the study who have liver biochemistry abnormalities or hepatic adverse events that first appeared during imetelstat treatment, or worsened from baseline during treatment, and were continuing at the time the patient stopped imetelstat treatment. Reversibility of these abnormalities back to normal or baseline levels after stopping imetelstat will be assessed.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
11 March 2014	On 11 March 2014 the United States (U.S.) Food and Drug Administration (FDA) informed Geron that the Imetelstat Investigational New Drug Application (IND) was being placed on a full clinical hold. Consequently, a communication was issued by Geron on 11 March 2014 to all Geron-sponsored imetelstat clinical trial sites with active patients, including Study CP14B015 sites, to immediately discontinue imetelstat treatment. The FDA cited the following safety issues as the basis for the clinical hold: lack of available evidence of reversibility of hepatotoxicity (i.e., hepatic biochemistry abnormalities or hepatic adverse events), the risk for chronic liver injury, and lack of adequate follow-up in patients who experienced hepatotoxicity. To address the clinical hold, Geron needs to provide clinical follow-up information in patients who experienced liver biochemistry abnormalities until those abnormalities have resolved to normal or baseline levels. Complete Response submitted by Geron on Oct 3 2014 and Full Clinical Hold lifted by FDA on Oct 31 2014.	31 October 2014

Notes:

Limitations and caveats

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

Enrollment in the Polycythemia Vera (PV) arm was limited to 2 patients out of the planned 20, since the Sponsor decided to redirect development in myeloid lineage neoplasms toward myelofibrosis, myelodysplastic syndromes and acute myeloid leukemia.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/26332546