



## Clinical trial results:

### A Randomized, Single-Blind, Multicenter Phase 2 Study to Evaluate the Activity of 2 Dose Levels of Imetelstat in Subjects with Intermediate-2 or High-Risk Myelofibrosis (MF) Relapsed/Refractory to Janus Kinase (JAK) Inhibitor

#### Summary

EudraCT number	2015-000946-41
Trial protocol	BE DE GB ES FR IT
Global end of trial date	07 February 2020

#### Results information

Result version number	v1 (current)
This version publication date	22 February 2021
First version publication date	22 February 2021

#### Trial information

##### Trial identification

Sponsor protocol code	63935937MYF2001
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02426086
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	Geron Corporation
Sponsor organisation address	919 E. Hillsdale Boulevard, Suite 250, Foster City, CA, United States, 94404
Public contact	Clinical Trial Enquiries, Geron Corporation, myf2001-info@Geron.com
Scientific contact	Clinical Trial Enquiries, Geron Corporation, myf2001-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	07 February 2020
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	07 February 2020
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The primary objectives of this study was to evaluate the efficacy and safety of 2 dose regimens of imetelstat (9.4 milligram/kilogram [mg/kg] and 4.7 mg/kg imetelstat given intravenous [IV] every 3 weeks) in subjects with intermediate-2 or high-risk MF who relapsed after or refractory to JAK inhibitor treatment.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 August 2015
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	Spain: 8
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	Belgium: 5
Country: Number of subjects enrolled	France: 8
Country: Number of subjects enrolled	Germany: 14
Country: Number of subjects enrolled	Italy: 14
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	Israel: 7
Country: Number of subjects enrolled	Korea, Republic of: 3
Country: Number of subjects enrolled	Taiwan: 1
Country: Number of subjects enrolled	United States: 42
Worldwide total number of subjects	107
EEA total number of subjects	53

Notes:

<b>Subjects enrolled per age group</b>	
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)	34
From 65 to 84 years	72
85 years and over	1

## Subject disposition

### Recruitment

Recruitment details:

Subjects were enrolled at 55 investigative sites in Belgium, Canada, France, Germany, Israel, Italy, Korea, Spain, Taiwan, United Kingdom, and the United States from 28 August 2015 to 25 October 2016. Data analyses include all data through the cut-off date 07 February 2020.

### Pre-assignment

Screening details:

A total of 107 subjects with Intermediate-2 or High-Risk Myelofibrosis (MF) Relapsed/Refractory to Janus Kinase (JAK) Inhibitor were randomly assigned to 1 of 2 treatment arms into 1:1 ratio to imetelstat 4.7 or imetelstat 9.4 mg/kg of body weight. Disposition data is reported till the end of study.

### Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Blinding implementation details:

Initially single-blind; treatments unmasked after 1st Interim Analysis and continued as open-label treatment.

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Imetelstat 4.7 mg/kg

Arm description:

Subjects received imetelstat 4.7 mg/kg of body weight as intravenous infusion on Day 1 of each 21-day cycle until disease progression, unacceptable toxicity, or study end. After the first interim analysis, treatment for all subjects was unblinded and subjects assigned to the imetelstat 4.7 mg/kg arm could continue with their same imetelstat dose or have it increased to 9.4 mg/kg at the investigator's discretion. After the end of main study, subjects who were receiving benefit from study treatment opted to continue to receive imetelstat during the Extension Phase until there is loss of benefit or unacceptable toxicity. (Maximum duration on study was approximately 2.3 years and Maximum duration on extension phase was approximately 1.8 years).

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

Dosage and administration details:

Subjects received imetelstat 4.7 mg/kg of body weight as intravenous infusion on Day 1 of each 21-day cycle until disease progression, unacceptable toxicity, or study end. After the first interim analysis, treatment for all subjects was unblinded and subjects assigned to the imetelstat 4.7 mg/kg arm could continue with their same imetelstat dose or have it increased to 9.4 mg/kg at the investigator's discretion. After the end of main study, subjects who were receiving benefit from study treatment opted to continue to receive imetelstat during the Extension Phase until there is loss of benefit or unacceptable toxicity.

<b>Arm title</b>	Imetelstat 9.4 mg/kg
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Arm description:

Subjects received imetelstat 9.4 mg/kg of body weight as intravenous infusion on Day 1 of each 21-days cycle until disease progression, unacceptable toxicity, or study end. After the end of the main study, subjects who were receiving benefit from study treatment opted to continue to receive imetelstat during the Extension Phase until there is loss of benefit or unacceptable toxicity. (Maximum duration on study was approximately 2.3 years and Maximum duration on extension phase was approximately 1.8 years).

Arm type	Experimental
Investigational medicinal product name	Imetelstat 9.4 mg/kg
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Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

**Dosage and administration details:**

Subjects received imetelstat 9.4 mg/kg of body weight as intravenous infusion on Day 1 of each 21-days cycle until disease progression, unacceptable toxicity, or study end. After the end of the main study, subjects who were receiving benefit from study treatment opted to continue to receive imetelstat during the Extension Phase until there is loss of benefit or unacceptable toxicity.

<b>Number of subjects in period 1</b>	Imetelstat 4.7 mg/kg	Imetelstat 9.4 mg/kg
Started	48	59
Treated	48	59
Completed	0	0
Not completed	48	59
Consent withdrawn by subject	8	9
Death	33	36
Study Terminated by Sponsor	5	14
Lost to follow-up	2	-

## Baseline characteristics

### Reporting groups

Reporting group title	Imetelstat 4.7 mg/kg
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Reporting group description:

Subjects received imetelstat 4.7 mg/kg of body weight as intravenous infusion on Day 1 of each 21-day cycle until disease progression, unacceptable toxicity, or study end. After the first interim analysis, treatment for all subjects was unblinded and subjects assigned to the imetelstat 4.7 mg/kg arm could continue with their same imetelstat dose or have it increased to 9.4 mg/kg at the investigator's discretion. After the end of main study, subjects who were receiving benefit from study treatment opted to continue to receive imetelstat during the Extension Phase until there is loss of benefit or unacceptable toxicity. (Maximum duration on study was approximately 2.3 years and Maximum duration on extension phase was approximately 1.8 years).

Reporting group title	Imetelstat 9.4 mg/kg
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Reporting group description:

Subjects received imetelstat 9.4 mg/kg of body weight as intravenous infusion on Day 1 of each 21-days cycle until disease progression, unacceptable toxicity, or study end. After the end of the main study, subjects who were receiving benefit from study treatment opted to continue to receive imetelstat during the Extension Phase until there is loss of benefit or unacceptable toxicity. (Maximum duration on study was approximately 2.3 years and Maximum duration on extension phase was approximately 1.8 years).

Reporting group values	Imetelstat 4.7 mg/kg	Imetelstat 9.4 mg/kg	Total
Number of subjects	48	59	107
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	68.0	66.5	
standard deviation	± 8.95	± 9.39	-
Gender categorical			
Units: Subjects			
Female	16	24	40
Male	32	35	67
Ethnicity			
Units: Subjects			
Hispanic or Latino	2	8	10
Not Hispanic or Latino	41	44	85
Unknown	2	3	5
Not Reported	3	4	7
Race			
Units: Subjects			
White	40	48	88
Black/African American	2	2	4
Asian	2	3	5
Multiple	1	0	1
Not Reported	3	6	9
Region			
Units: Subjects			
United States/Canada	25	18	43
European Union	19	34	53

Rest of World	4	7	11
Platelet Count			
Units: Subjects			
<75 (10 <sup>9</sup> /L)	1	2	3
75 - <150 (10 <sup>9</sup> /L)	23	31	54
≥150 (10 <sup>9</sup> /L)	24	26	50
ECOG Score			
Eastern Cooperative Oncology Group (ECOG) Score has 5 grades.0= Fully active, able to carry on all predisease performance without restriction;1= Restricted in physically strenuous activity but ambulatory, able to carry out work on a light or sedentary nature, eg, light housework, office work;2= Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about > 50% of waking hours;3= Capable of only limited self-care; confined to bed or chair > 50% of waking hours;4= Completely disabled. Cannot carry on any self-care.Totally confined to bed or chair;5=Dead.			
Units: Subjects			
0: Asymptomatic	11	14	25
1: Symptomatic fully ambulatory	26	34	60
2: Self care	11	11	22
DIPSS Score			
The Dynamic International Prognostic Scoring System (DIPSS) stratifies primary myelofibrosis (PMF) into four risk categories (low, intermediate 1, intermediate 2, and high risk), based on 5 clinical factors; Age>65, Hemoglobin <10gm/dL, Leukocytes >10 (9)/L, circulating blasts ≥1%, and constitutional symptoms.			
Units: Subjects			
Intermediate 2	28	34	62
High Risk	19	25	44
Missing	1	0	1
Type of MF			
Units: Subjects			
Primary MF (PMF)	27	36	63
Post Essential Thrombocythemia (PET)	9	10	19
Post Polycythemia Vera (PPV)	12	13	25
Spleen Size by Palpation			
Number (N= 47 for reporting group 1) analyzed signifies the number of subjects with data available for spleen size palpitation.			
Units: centimeter (cm)			
arithmetic mean	17.6	17.3	
standard deviation	± 7.62	± 7.51	-
Time from Last JAKi Treatment			
Units: months			
median	1.4	1.7	
full range (min-max)	1 to 31	1 to 38	-
Duration of Prior JAKi Treatment			
Units: months			
median	22.3	24.5	
full range (min-max)	3 to 90	1 to 73	-

## End points

### End points reporting groups

Reporting group title	Imetelstat 4.7 mg/kg
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Reporting group description:

Subjects received imetelstat 4.7 mg/kg of body weight as intravenous infusion on Day 1 of each 21-day cycle until disease progression, unacceptable toxicity, or study end. After the first interim analysis, treatment for all subjects was unblinded and subjects assigned to the imetelstat 4.7 mg/kg arm could continue with their same imetelstat dose or have it increased to 9.4 mg/kg at the investigator's discretion. After the end of main study, subjects who were receiving benefit from study treatment opted to continue to receive imetelstat during the Extension Phase until there is loss of benefit or unacceptable toxicity. (Maximum duration on study was approximately 2.3 years and Maximum duration on extension phase was approximately 1.8 years).

Reporting group title	Imetelstat 9.4 mg/kg
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Reporting group description:

Subjects received imetelstat 9.4 mg/kg of body weight as intravenous infusion on Day 1 of each 21-days cycle until disease progression, unacceptable toxicity, or study end. After the end of the main study, subjects who were receiving benefit from study treatment opted to continue to receive imetelstat during the Extension Phase until there is loss of benefit or unacceptable toxicity. (Maximum duration on study was approximately 2.3 years and Maximum duration on extension phase was approximately 1.8 years).

Subject analysis set title	PK: Imetelstat 4.7 mg/kg
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

Subjects received imetelstat 4.7 mg/kg of body weight as intravenous infusion on Day 1 of cycle 1 and those who had serial PK samples collected.

Subject analysis set title	PK: Imetelstat 9.4 mg/kg
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

Subjects received imetelstat 9.4 mg/kg of body weight as intravenous infusion on Day 1 of cycle 1 and those who had serial PK samples collected.

### Primary: Percentage of Subjects with Spleen Response

End point title	Percentage of Subjects with Spleen Response <sup>[1]</sup>
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End point description:

Spleen response rate is defined as the percentage of subjects who achieved  $\geq 35\%$  reduction in spleen volume at Week 24 from baseline performed by the IRC using magnetic resonance imaging (MRI). Treated analysis set included all subjects who received at least 1 dose of study drug.

End point type	Primary
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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: The percentage and 95% CI are the statistical analysis per protocol.

End point values	Imetelstat 4.7 mg/kg	Imetelstat 9.4 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	59		
Units: percentage of subjects				
number (confidence interval 95%)	0 (0 to 7.4)	10.2 (3.8 to 20.8)		



## Statistical analyses

No statistical analyses for this end point

### Primary: Percentage of Subjects with Symptom Response

End point title	Percentage of Subjects with Symptom Response <sup>[2]</sup>
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End point description:

Symptom response rate is defined as percentage of subjects who achieved  $\geq 50\%$  reduction in total symptom score (TSS) at Week 24 from baseline as measured by the modified Myelofibrosis Symptom Assessment Form (MFSAF) version 2.0 diary. The MFSAF assessed following symptoms due to Myelofibrosis (MF): night sweats, itchiness, abdominal discomfort, pain under ribs on left side, feeling of fullness, bone or muscle pain and degree of inactivity. Each item is scored on a scale of 0 (absent) to 10 (worst imaginable) with higher scores indicating more severe symptoms and greater inactivity. The total score ranges from 0-70, where 0 indicates absent/as good as it can be and 70 indicates worst imaginable/as bad as it can be. Treated analysis set included all subjects who received at least 1 dose of study drug.

End point type	Primary
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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: The percentage and 95% CI are the statistical analysis per protocol.

End point values	Imetelstat 4.7 mg/kg	Imetelstat 9.4 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	59		
Units: percentage of subjects				
number (confidence interval 95%)	6.3 (1.3 to 17.2)	32.2 (20.6 to 45.6)		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects With Overall Response as Per Modified 2013 International Working Group - Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) Criteria

End point title	Percentage of Subjects With Overall Response as Per Modified 2013 International Working Group - Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) Criteria
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End point description:

Overall response rate (ORR): % of subjects with complete remission (CR) or partial R (PR). CR: bone marrow (BM): normocellular  $<5\%$  blasts,  $\leq$  Grade 1 fibrosis; immature myeloid cells (IMC) in peripheral blood (PB):  $<2\%$ ; Hb: 10 g/dL-upper limit of normal (ULN); neutrophils:  $1 \times 10^9/\text{L}$ -ULN; platelets:  $100 \times 10^9/\text{L}$ -ULN; spleen: not palpable and  $\leq 350\text{ml}$  volume; extramedullary hematopoiesis (EMH): no non-hepato-splenic EMH; symptoms:  $>70\%$  improvement in symptom score. PR: BM: normocellular:

<5% blasts ≤Grade 1 fibrosis/not meeting BM remission criteria; IMC in PB: <2%; Hb: 8.5 -<10 g/dL-ULN or 10 g/dL-ULN; neutrophils:  $1 \times 10^9/L$ -ULN; platelets: 50 -< $100 \times 10^9/L$ -ULN; spleen: ≥35% splenic volumetric reduction by MRI/not palpable; EMH: no non-hepato-splenic EMH; symptoms: >50% improvement in symptom score. Response categories benefit last >12 weeks to qualify as response. Treated analysis set was used. Upper and lower limits of 95% CI not estimable due to limited number of events and indicate by 99999.

End point type	Secondary
End point timeframe:	
Every 12 weeks up to Week 48 then every 24 weeks (approximately up to 2.3 years)	

End point values	Imetelstat 4.7 mg/kg	Imetelstat 9.4 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	59		
Units: percentage of subjects				
number (confidence interval 95%)	0 (-99999 to 99999)	1.7 (0.0 to 9.1)		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Subjects With Clinical Improvement (CI) Per Modified 2013 IWG-MRT Criteria

End point title	Percentage of Subjects With Clinical Improvement (CI) Per Modified 2013 IWG-MRT Criteria
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End point description:

CI per the modified 2013 IWG-MRT criteria defined as the achievement of anemia, spleen or symptoms response without progressive disease or increase in severity of anemia, thrombocytopenia, or neutropenia (Increase in severity of anemia constitutes the occurrence of new transfusion dependency or a  $\geq 2.0$  g/dL decrease in hemoglobin level from pretreatment baseline that lasts for at least 12 weeks. Increase in severity of thrombocytopenia or neutropenia is defined as a 2-grade decline, from pretreatment baseline, in platelet count or ANC, according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03. In addition, assignment to CI requires a minimum platelet count of  $\geq 25,000 \times 10^9/L$  and ANC of  $\geq 0.5 \times 10^9/L$ .) For all response categories, benefit must last for >12 weeks to qualify as a response. Treated analysis set: subjects who received  $\geq 1$  dose of study drug.

End point type	Secondary
End point timeframe:	
Every 12 weeks up to Week 48 then every 24 weeks (approximately up to 2.3 years)	

End point values	Imetelstat 4.7 mg/kg	Imetelstat 9.4 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	59		
Units: percentage of subjects				
number (not applicable)	16.7	25.4		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects With Clinical Response Per Modified 2013 IWG-MRT

End point title	Percentage of Subjects With Clinical Response Per Modified 2013 IWG-MRT
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End point description:

Clinical response rate (CRR): % of subjects who achieved CR, PR, or CI per modified 2013 IWG-MRT criteria. CR: bone marrow: normocellular <5% blasts, ≤Grade 1 fibrosis; immature myeloid cells in PB: <2%; Hb: 10 g/dL-ULN; neutrophils:  $1 \times 10^9$ /L-ULN; platelets:  $100 \times 10^9$ /L-ULN; spleen: not palpable and ≤350ml volume; EMH: no non-hepato-splenic EMH; symptoms: >70% improvement in symptom score. PR: bone marrow: normocellular: <5% blasts ≤ Grade 1 fibrosis or not meeting bone marrow remission criteria; Immature myeloid cells in PB: <2%; Hb: 8.5 -<10 g/dL-ULN or 10 g/dL-ULN; neutrophils:  $1 \times 10^9$ /L-ULN; platelets: 50 -< $100 \times 10^9$ /L-ULN; spleen: ≥35% splenic volumetric reduction by MRI or not palpable; EMH: no non-hepato-splenic EMH; symptoms: >50% improvement in symptom score. CI: achievement of anemia, spleen or symptoms response without PD or increase in severity of anemia, thrombocytopenia, or neutropenia. Treated analysis set: subjects who received ≥ 1 dose of study drug.

End point type	Secondary
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End point timeframe:

Every 12 weeks up to Week 48 then every 24 weeks (approximately up to 2.3 years)

End point values	Imetelstat 4.7 mg/kg	Imetelstat 9.4 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	59		
Units: percentage of subjects				
number (confidence interval 95%)	16.7 (7.5 to 30.2)	27.1 (16.4 to 40.3)		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects With Spleen Response Per Modified 2013 IWG-MRT Criteria

End point title	Percentage of Subjects With Spleen Response Per Modified 2013 IWG-MRT Criteria
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End point description:

Spleen response per modified 2013 IWG-MRT criteria. Spleen response: a baseline splenomegaly that is palpable at 5-10 cm, below the left costal margin (LCM), becomes not palpable or a baseline splenomegaly that is palpable at >10 cm, below the LCM, decreases by ≥ 50%; A spleen response requires confirmation by MRI showing >35% spleen volume reduction (SVR). For response categories,

benefit must last for >12 weeks to qualify as a response. Subjects who achieved CI per modified IWG-MRT criteria considered as response with clinical improvement. Subjects who met criteria for spleen response but had worsening cytopenias (and therefore did not meet criteria for clinical improvement) were considered to have a response without clinical improvement. Treated analysis set included all subjects who received at least 1 dose of study drug.

End point type	Secondary
End point timeframe:	
Every 12 weeks up to Week 48 then every 24 weeks (approximately up to 2.3 years)	

End point values	Imetelstat 4.7 mg/kg	Imetelstat 9.4 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	59		
Units: percentage of subjects				
number (not applicable)				
CI Response: Spleen response	0	3.4		
Response without CI: Spleen response	2.1	0		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Subjects With Symptom Response Per Modified 2013 IWG-MRT Criteria

End point title	Percentage of Subjects With Symptom Response Per Modified 2013 IWG-MRT Criteria
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End point description:

Symptom response per modified 2013 IWG-MRT criteria. Symptoms Response: a  $\geq 50\%$  reduction in the modified MFSAF v2.0 TSS. For response category, benefit must last for >12 weeks to qualify as a response. Subjects who achieved CI per modified IWG-MRT criteria considered as response with clinical improvement. Subjects who met criteria for symptom response but had worsening cytopenias (and therefore did not meet criteria for clinical improvement) were considered to have a response without clinical improvement. Treated analysis set included all subjects who received at least 1 dose of study drug.

End point type	Secondary
End point timeframe:	
Every 12 weeks up to Week 48 then every 24 weeks (approximately up to 2.3 years)	

End point values	Imetelstat 4.7 mg/kg	Imetelstat 9.4 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	59		
Units: percentage of subjects				
number (not applicable)				
CI Response: Spleen response	14.6	22.0		
Response without CI: Spleen response	4.2	8.5		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects With Anemia Response Per Modified 2013 IWG-MRT Criteria

End point title	Percentage of Subjects With Anemia Response Per Modified 2013 IWG-MRT Criteria
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End point description:

Anemia response per modified 2013 IWG-MRT criteria. Anemia response is defined as subjects with baseline Hb <10 g/dL but not meeting strict criteria for transfusion dependency: a  $\geq 2$  g/dL increase in Hb; Transfusion dependent subjects at baseline: becoming transfusion independent. Transfusion independence is defined as absence of any pRBC transfusions for at least 12 "rolling" weeks. For response categories, benefit must last for >12 weeks to qualify as a response. Subjects who achieved CI per modified IWG-MRT criteria considered as response with clinical improvement. Subjects who met criteria for anemia response but had worsening cytopenias (and therefore did not meet criteria for clinical improvement) were considered to have a response without clinical improvement. Treated analysis set included all subjects who received at least 1 dose of study drug.

End point type	Secondary
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End point timeframe:

Every 12 weeks up to Week 48 then every 24 weeks (approximately up to 2.3 years)

End point values	Imetelstat 4.7 mg/kg	Imetelstat 9.4 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	59		
Units: percentage of subjects				
number (not applicable)				
CI Response: Spleen response	4.2	6.8		
Response without CI: Spleen response	0	1.7		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Duration of Response (PR/CI/RWCI) as Per IWG-MRT Criteria

End point title	Duration of Response (PR/CI/RWCI) as Per IWG-MRT Criteria
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End point description:

Duration of response (PR/CI/RWCI) is the duration from the date of initial documentation of a response to date of first documented evidence of PD or death, whichever occurs first. PR: BM: normocellular: <5% blasts  $\leq$  Grade 1 fibrosis/not meeting BM remission criteria; IMC in PB: <2%; Hb: 8.5 -<10 g/dL-ULN or 10 g/dL-ULN; neutrophils:  $1 \times 10^9$ /L-ULN; platelets: 50 -<100  $\times 10^9$ /L-ULN; spleen:  $\geq 35\%$  splenic volumetric reduction by MRI/not palpable; EMH: no non-hepato-splenic EMH; symptoms: >50% improvement in symptom score. CI: achievement of anemia, spleen or symptoms response without PD

or increase in severity of anemia, thrombocytopenia, neutropenia. RWCI: Subjects who met criteria for response but had worsening cytopenias. PD: Splenomegaly requires MRI showing  $\geq 25\%$  increase in spleen volume. Treated analysis set included all subjects who received at least 1 dose of study drug. Overall number of subjects analysed ("N") = subjects who were responders (PR/CI/RWCI) at any time.

End point type	Secondary
End point timeframe:	
From date of initial documentation of a response to the date of first documented evidence of PD or death, whichever occurs first (approximately up to 2.3 years)	

End point values	Imetelstat 4.7 mg/kg	Imetelstat 9.4 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	21		
Units: weeks				
median (confidence interval 95%)	36.3 (11.9 to 60.0)	38.3 (27.0 to 48.3)		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Overall Survival

End point title	Overall Survival
End point description:	
Overall Survival is measured from the date of Cycle 1, Day 1 to the date of the subject's death. If the subject was alive or the vital status was unknown, OS was censored at the date that the subject is last known to be alive. Treated analysis set included all subjects who received at least 1 dose of study drug.	
End point type	Secondary
End point timeframe:	
Day 1 of Cycle 1 (each cycle was of 21 days) up to the date of the subject's death (approximately up to 4.1 years)	

End point values	Imetelstat 4.7 mg/kg	Imetelstat 9.4 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	59		
Units: months				
median (confidence interval 95%)	19.91 (17.05 to 33.87)	28.09 (22.80 to 31.61)		

## Statistical analyses

No statistical analyses for this end point

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**Secondary: Percentage of Subjects with Clinically Meaningful Improvement in European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-30 (QLQ-C30): Global Health Status**

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End point title	Percentage of Subjects with Clinically Meaningful Improvement in European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-30 (QLQ-C30): Global Health Status
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End point description:

EORTC QLQ-C30 is a questionnaire to assess quality of life of cancer subjects. EORTC QLQ-C30 included 30 items resulting in 5 functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning), 3 symptom scales (fatigue, nausea and vomiting, and pain), and 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties) which are based on 4-point scale (1= Not at all to 4= Very much); and 1 global health status scale based on 7-point scale (1= Very poor to 7= Excellent). All scales and items are averaged, transformed to 0-100 scale; higher score=better level of functioning. Clinically meaningful improvement defined as change greater than half of the standard deviation at baseline in QLQ-C30 Global Health Status. Treated analysis set included all subjects who received at least 1 dose of study drug. Here "N"= subjects who had data at both baseline and end of treatment.

End point type	Secondary
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End point timeframe:

Up to end of the treatment (approximately up to 2.3 years)

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End point values	Imetelstat 4.7 mg/kg	Imetelstat 9.4 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	33		
Units: percentage of subjects				
number (not applicable)				
Improvement	22.2	36.4		

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**Statistical analyses**

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No statistical analyses for this end point

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**Secondary: EuroQol 5 Dimension 5 Level (EQ-5D-5L): Utility Score and Visual Analog Scale (VAS)**

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End point title	EuroQol 5 Dimension 5 Level (EQ-5D-5L): Utility Score and Visual Analog Scale (VAS)
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End point description:

EQ-5D-5L is standardized health-related quality of life questionnaire developed by EuroQol Group to provide a simple, generic measure of health for clinical and economic appraisal. EQ-5D-5L consists of two components: health state profile and VAS. EQ-5D health state profile comprises of 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: 1=no problems, 2=slight problems, 3=moderate problems, 4=severe problems, and 5=extreme problems. 5D-5L systems are converted into single index utility score between 0 to 1, where higher score indicates a better health state. EQ-5D-5L- VAS is designed to rate subject's current health state on scale from 0 to 100, where 0 represents worst imaginable health state and 100 represents best imaginable health state. Treated analysis set was used. "n"= number of subjects with data available for each specified category and "N"= subjects who had data at both baseline and end of treatment.

End point type	Secondary
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End point timeframe:

Baseline up to end of treatment (approximately up to 2.3 years)

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<b>End point values</b>	Imetelstat 4.7 mg/kg	Imetelstat 9.4 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	33		
Units: score on scale				
arithmetic mean (standard deviation)				
EQ-5D-5L : Utility Score (n= 18, 32)	0.498 (± 0.2999)	0.626 (± 0.2117)		
EQ-5D-5L :VAS (n= 18, 33)	51.28 (± 21.143)	47.73 (± 16.398)		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Subjects With Clinically Meaningful Improvement in Brief Pain Inventory (BPI)

End point title	Percentage of Subjects With Clinically Meaningful Improvement in Brief Pain Inventory (BPI)
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End point description:

The BPI rates the intensity of pain on 4 items (right now, worst, least, and average), and the interference in 7 areas (general activity, mood, walking ability, normal work, relations, sleep, enjoyment of life). Minimum value = 0; maximum value = 10. Higher scores indicate greater symptom severity/worse outcomes. Clinically meaningful improvement (Imp) in BPI defined as change greater than half of the standard deviation at baseline. Treated analysis set included all subjects who received at least 1 dose of study drug. Here, "N" signifies number of subjects who had data at both baseline and end of treatment and "n" is the number of subjects with data available for each specified category.

End point type	Secondary
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End point timeframe:

Up to end of treatment (approximately up to 2.3 years)

<b>End point values</b>	Imetelstat 4.7 mg/kg	Imetelstat 9.4 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	33		
Units: percentage of subjects				
number (not applicable)				
Pain at its Worst:Imp(n=18,33)	50.0	75.8		
Pain at its Least:Imp(n=18,33)	44.4	51.5		
Pain on the Average:Imp(n=18,33)	55.6	66.7		
Pain Right Now:Imp(n=18,33)	61.1	66.7		
Relief Pain Treatments Provided:Imp(n=18,32)	50.0	53.1		
Pain Interfered General Activity:Imp(n=18,32)	72.2	68.8		
Pain Interfered with Mood:Imp(n=18,32)	50.0	59.4		



Pain Interfered Walking Ability:Imp(n=18,32)	38.9	78.1		
Pain Interfered with Normal Work:Imp(n=18,32)	61.1	62.5		
Pain Interfered with Relations:Imp(n=18,32)	44.4	53.1		
Pain Interfered with Sleep:Imp(n=18,32)	61.1	78.1		
Pain Interfered Enjoyment of Life:Imp(n=18,32)	61.1	62.5		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Patient's Global Impression of Change (PGIC)

End point title	Patient's Global Impression of Change (PGIC)
End point description:	
The PGIC was used to capture the subject's perspective of improvement or decline in MF symptoms over time. The PGIC had a 7-point response scale ranging from 1 to 7 where, 1=very much improved, 2=somewhat improved, 3= a little improved, 4=no change, 5= a little worse, 6= somewhat worse, 7=very much worse. Treated analysis set included all subjects who received at least 1 dose of study drug. Here, "N" signifies number of subjects who had data at both baseline and end of treatment.	
End point type	Secondary
End point timeframe:	
Up to end of treatment (approximately up to 2.3 years)	

End point values	Imetelstat 4.7 mg/kg	Imetelstat 9.4 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	33		
Units: score on a scale				
arithmetic mean (standard deviation)	4.82 (± 1.237)	3.97 (± 1.571)		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Subjects with Treatment-emergent Adverse Events (TEAEs)

End point title	Number of Subjects with Treatment-emergent Adverse Events (TEAEs)
End point description:	
An AE is any untoward medical occurrence in a subject or clinical investigation subjects administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. TEAEs were AEs with onset during or after the first dose of study drug, and within 30 days following the last dose of study drug. Safety analysis set included all subjects who received at least 1 dose of study treatment.	
End point type	Secondary

End point timeframe:

Up to end of extension phase (approximately up to 4.2 years)

End point values	Imetelstat 4.7 mg/kg	Imetelstat 9.4 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	59		
Units: subjects				
number (not applicable)	47	59		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Maximum Observed Plasma Concentration (C<sub>max</sub>) of Imetelstat

End point title	Maximum Observed Plasma Concentration (C <sub>max</sub> ) of Imetelstat
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End point description:

Pharmacokinetic (PK) subset included all subjects who had serial PK sampling during cycle 1 treatment to determine the maximum plasma concentration of Imetelstat by noncompartmental PK analysis.

End point type	Secondary
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End point timeframe:

0 (before start of infusion), 1, 2, 3-5, 6-10, 12-16 and 18-24 hours post dose on Day 1 of Cycle 1 (each cycle was of 21 days)

End point values	PK: Imetelstat 4.7 mg/kg	PK: Imetelstat 9.4 mg/kg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11	17		
Units: µg/mL				
arithmetic mean (standard deviation)	57.0 (± 72.3)	81.9 (± 40.0)		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Time to Reach Maximum Observed Plasma Concentration (T<sub>max</sub>) of Imetelstat

End point title	Time to Reach Maximum Observed Plasma Concentration (T <sub>max</sub> ) of Imetelstat
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End point description:

PK subset included all subjects who had serial PK sampling during cycle 1 treatment to determine the time to reach maximum plasma concentration of imetelstat by noncompartmental PK analysis.

End point type	Secondary
End point timeframe:	
0 (before start of infusion), 1, 2, 3-5, 6-10, 12-16 and 18-24 hours post dose on Day 1 of Cycle 1 (each cycle was of 21 days)	

<b>End point values</b>	PK: Imetelstat 4.7 mg/kg	PK: Imetelstat 9.4 mg/kg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11	17		
Units: hr				
median (full range (min-max))	2.00 (1.93 to 2.20)	2.00 (1.00 to 2.75)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Area Under the Plasma Concentration-Time Curve From Time Zero to 24 Hours (AUC 0-24) of Imetelstat

End point title	Area Under the Plasma Concentration-Time Curve From Time Zero to 24 Hours (AUC 0-24) of Imetelstat
End point description:	
PK subset included all subjects who had serial PK sampling during cycle 1 treatment to determine the AUC 0-24 of Imetelstat by noncompartmental PK analysis.	
End point type	Secondary
End point timeframe:	
0 (before start of infusion), 1, 2, 3-5, 6-10, 12-16 and 18-24 hours post dose on Day 1 of Cycle 1 (each cycle was of 21 days)	

<b>End point values</b>	PK: Imetelstat 4.7 mg/kg	PK: Imetelstat 9.4 mg/kg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11	17		
Units: µg*hr/mL				
arithmetic mean (standard deviation)	171 (± 135)	501 (± 283)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Area Under the Plasma Concentration-Time Profile From Time Zero to Infinity (AUC0-inf) of Imetelstat

End point title	Area Under the Plasma Concentration-Time Profile From Time Zero to Infinity (AUC0-inf) of Imetelstat
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End point description:

PK subset included all subjects who had serial PK sampling during cycle 1 treatment to determine AUC 0-inf of Imetelstat by noncompartmental PK analysis.

End point type	Secondary
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End point timeframe:

0 (before start of infusion), 1, 2, 3-5, 6-10, 12-16 and 18-24 hours post dose on Day 1 of Cycle 1 (each cycle was of 21 days)

End point values	PK: Imetelstat 4.7 mg/kg	PK: Imetelstat 9.4 mg/kg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11	17		
Units: µg*hr/mL				
arithmetic mean (standard deviation)	193 (± 156)	524 (± 297)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Elimination Half-Life (t<sub>1/2</sub>) of Imetelstat

End point title	Elimination Half-Life (t <sub>1/2</sub> ) of Imetelstat
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End point description:

Elimination half-life (t<sub>1/2</sub>) is associated with the terminal slope (lambda [z]) of the semi logarithmic drug concentration-time curve, calculated as 0.693/lambda(z). PK subset included all subjects who had serial PK sampling during cycle 1 treatment to determine the t<sub>1/2</sub> of Imetelstat by noncompartmental PK analysis.

End point type	Secondary
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End point timeframe:

0 (before start of infusion), 1, 2, 3-5, 6-10, 12-16 and 18-24 hours post dose on Day 1 of Cycle 1 (each cycle was of 21 days)

End point values	PK: Imetelstat 4.7 mg/kg	PK: Imetelstat 9.4 mg/kg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11	17		
Units: hr				
arithmetic mean (standard deviation)	4.6 (± 1.6)	5.5 (± 1.5)		

### Statistical analyses

No statistical analyses for this end point

**Secondary: Total Systemic Clearance (CL) of Imetelstat**

End point title	Total Systemic Clearance (CL) of Imetelstat
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End point description:

PK subset included all subjects who had serial PK sampling during cycle 1 treatment to determine the CL of Imetelstat by noncompartmental PK analysis.

End point type	Secondary
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End point timeframe:

0 (before start of infusion), 1, 2, 3-5, 6-10, 12-16 and 18-24 hours post dose on Day 1 of Cycle 1 (each cycle was of 21 days)

End point values	PK: Imetelstat 4.7 mg/kg	PK: Imetelstat 9.4 mg/kg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11	17		
Units: L/hr/kg				
arithmetic mean (standard deviation)	0.0329 ( $\pm$ 0.0138)	0.0252 ( $\pm$ 0.0157)		

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Volume of Distribution (Vd) of Imetelstat**

End point title	Volume of Distribution (Vd) of Imetelstat
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End point description:

PK population analysis set included all subjects who received at least 1 dose of study drug and had at least 1 sample collected during treatment to determine the drug concentration.

End point type	Secondary
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End point timeframe:

0 (before start of infusion), 1, 2, 3-5, 6-10, 12-16 and 18-24 hours post dose on Day 1 of Cycle 1 (each cycle was of 21 days)

End point values	PK: Imetelstat 4.7 mg/kg	PK: Imetelstat 9.4 mg/kg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11	17		
Units: L/kg				
arithmetic mean (standard deviation)	0.198 ( $\pm$ 0.0770)	0.190 ( $\pm$ 0.104)		

**Statistical analyses**

No statistical analyses for this end point



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Up to end of extension phase (approximately up to 4.2 years)

Adverse event reporting additional description:

Safety analysis set included all subjects who received at least 1 dose of study treatment.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	21.1
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### Reporting groups

Reporting group title	Imetelstat 4.7 mg/kg
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Reporting group description:

Subjects received imetelstat 4.7 mg/kg of body weight as intravenous infusion on Day 1 of each 21-day cycle until disease progression, unacceptable toxicity, or study end. After the first interim analysis, treatment for all subjects was unblinded and subjects assigned to the imetelstat 4.7 mg/kg arm could continue with their same imetelstat dose or have it increased to 9.4 mg/kg at the investigator's discretion.

After the end of main study, subjects who were receiving benefit from study treatment opted to continue to receive imetelstat during the Extension Phase until there is loss of benefit or unacceptable toxicity. (Maximum duration on study was approximately 2.3 years and Maximum duration on extension phase was approximately 1.8 years).

Reporting group title	Imetelstat 9.4 mg/kg
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Reporting group description:

Subjects received imetelstat 9.4 mg/kg of body weight as intravenous infusion on Day 1 of each 21-days cycle until disease progression, unacceptable toxicity, or study end. After the end of the main study, subjects who were receiving benefit from study treatment opted to continue to receive imetelstat during the Extension Phase until there is loss of benefit or unacceptable toxicity. (Maximum duration on study was approximately 2.3 years and Maximum duration on extension phase was approximately 1.8 years).

Serious adverse events	Imetelstat 4.7 mg/kg	Imetelstat 9.4 mg/kg	
Total subjects affected by serious adverse events			
subjects affected / exposed	21 / 48 (43.75%)	24 / 59 (40.68%)	
number of deaths (all causes)	35	36	
number of deaths resulting from adverse events	3	3	
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 48 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Injury, poisoning and procedural complications			
Head injury			

subjects affected / exposed	1 / 48 (2.08%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
<b>Vascular disorders</b>			
Aneurysm ruptured			
subjects affected / exposed	0 / 48 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Haematoma</b>			
subjects affected / exposed	1 / 48 (2.08%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Haemorrhage</b>			
subjects affected / exposed	0 / 48 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
<b>Cardiac disorders</b>			
Cardiac failure			
subjects affected / exposed	1 / 48 (2.08%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Cardiac failure congestive			
subjects affected / exposed	1 / 48 (2.08%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac tamponade			
subjects affected / exposed	0 / 48 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Blood and lymphatic system disorders</b>			
Anaemia			
subjects affected / exposed	0 / 48 (0.00%)	2 / 59 (3.39%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	



Bone marrow failure			
subjects affected / exposed	0 / 48 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	1 / 48 (2.08%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemolysis			
subjects affected / exposed	0 / 48 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytosis			
subjects affected / exposed	1 / 48 (2.08%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	0 / 48 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic artery thrombosis			
subjects affected / exposed	1 / 48 (2.08%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic infarction			
subjects affected / exposed	2 / 48 (4.17%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Splenic vein thrombosis			
subjects affected / exposed	1 / 48 (2.08%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenomegaly			

subjects affected / exposed	1 / 48 (2.08%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 48 (2.08%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chills			
subjects affected / exposed	1 / 48 (2.08%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	0 / 48 (0.00%)	2 / 59 (3.39%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	1 / 48 (2.08%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	0 / 48 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 48 (4.17%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	0 / 48 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Diarrhoea			
subjects affected / exposed	1 / 48 (2.08%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	0 / 48 (0.00%)	2 / 59 (3.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	0 / 48 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 48 (2.08%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	0 / 48 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic function abnormal			
subjects affected / exposed	1 / 48 (2.08%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 48 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Dyspnoea			
subjects affected / exposed	4 / 48 (8.33%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	2 / 5	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pleural effusion			
subjects affected / exposed	0 / 48 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary congestion			
subjects affected / exposed	1 / 48 (2.08%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary hypertension			
subjects affected / exposed	0 / 48 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	1 / 48 (2.08%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 48 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	0 / 48 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bacterial infection			
subjects affected / exposed	0 / 48 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 48 (2.08%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cellulitis			
subjects affected / exposed	1 / 48 (2.08%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia bacteraemia			
subjects affected / exposed	1 / 48 (2.08%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Listeriosis			
subjects affected / exposed	0 / 48 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	1 / 48 (2.08%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ophthalmic herpes zoster			
subjects affected / exposed	0 / 48 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 48 (4.17%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia klebsiella			
subjects affected / exposed	0 / 48 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 48 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			

subjects affected / exposed	1 / 48 (2.08%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 48 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 48 (2.08%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Failure to thrive			
subjects affected / exposed	0 / 48 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid overload			
subjects affected / exposed	0 / 48 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gout			
subjects affected / exposed	1 / 48 (2.08%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	0 / 48 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

<b>Non-serious adverse events</b>	Imetelstat 4.7 mg/kg	Imetelstat 9.4 mg/kg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	47 / 48 (97.92%)	59 / 59 (100.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 48 (6.25%)	4 / 59 (6.78%)	
occurrences (all)	5	4	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	9 / 48 (18.75%)	14 / 59 (23.73%)	
occurrences (all)	11	21	
Chills			
subjects affected / exposed	3 / 48 (6.25%)	8 / 59 (13.56%)	
occurrences (all)	7	15	
Fatigue			
subjects affected / exposed	10 / 48 (20.83%)	15 / 59 (25.42%)	
occurrences (all)	14	20	
Malaise			
subjects affected / exposed	2 / 48 (4.17%)	3 / 59 (5.08%)	
occurrences (all)	2	5	
Oedema peripheral			
subjects affected / exposed	13 / 48 (27.08%)	10 / 59 (16.95%)	
occurrences (all)	18	12	
Pain			
subjects affected / exposed	1 / 48 (2.08%)	3 / 59 (5.08%)	
occurrences (all)	1	5	
Pyrexia			
subjects affected / exposed	8 / 48 (16.67%)	13 / 59 (22.03%)	
occurrences (all)	14	24	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	11 / 48 (22.92%)	9 / 59 (15.25%)	
occurrences (all)	17	12	
Dyspnoea			
subjects affected / exposed	7 / 48 (14.58%)	15 / 59 (25.42%)	
occurrences (all)	8	22	

Epistaxis subjects affected / exposed occurrences (all)	3 / 48 (6.25%) 3	1 / 59 (1.69%) 1	
Oropharyngeal pain subjects affected / exposed occurrences (all)	5 / 48 (10.42%) 5	4 / 59 (6.78%) 5	
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	6 / 48 (12.50%) 7	7 / 59 (11.86%) 8	
Investigations Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	2 / 48 (4.17%) 2	5 / 59 (8.47%) 7	
Serum ferritin increased subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	4 / 59 (6.78%) 5	
Weight decreased subjects affected / exposed occurrences (all)	9 / 48 (18.75%) 12	8 / 59 (13.56%) 14	
Injury, poisoning and procedural complications Fall subjects affected / exposed occurrences (all)	3 / 48 (6.25%) 3	2 / 59 (3.39%) 3	
Cardiac disorders Palpitations subjects affected / exposed occurrences (all)	2 / 48 (4.17%) 5	6 / 59 (10.17%) 7	
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	2 / 48 (4.17%) 2	10 / 59 (16.95%) 13	
Headache subjects affected / exposed occurrences (all)	6 / 48 (12.50%) 8	10 / 59 (16.95%) 14	
Blood and lymphatic system disorders			



Anaemia			
subjects affected / exposed	15 / 48 (31.25%)	26 / 59 (44.07%)	
occurrences (all)	35	95	
Leukocytosis			
subjects affected / exposed	3 / 48 (6.25%)	2 / 59 (3.39%)	
occurrences (all)	6	3	
Leukopenia			
subjects affected / exposed	3 / 48 (6.25%)	8 / 59 (13.56%)	
occurrences (all)	12	30	
Neutropenia			
subjects affected / exposed	5 / 48 (10.42%)	21 / 59 (35.59%)	
occurrences (all)	13	72	
Splenomegaly			
subjects affected / exposed	0 / 48 (0.00%)	3 / 59 (5.08%)	
occurrences (all)	0	3	
Thrombocytopenia			
subjects affected / exposed	11 / 48 (22.92%)	29 / 59 (49.15%)	
occurrences (all)	26	121	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	2 / 48 (4.17%)	5 / 59 (8.47%)	
occurrences (all)	3	6	
Abdominal distension			
subjects affected / exposed	2 / 48 (4.17%)	4 / 59 (6.78%)	
occurrences (all)	5	7	
Abdominal pain			
subjects affected / exposed	9 / 48 (18.75%)	14 / 59 (23.73%)	
occurrences (all)	9	21	
Abdominal pain upper			
subjects affected / exposed	2 / 48 (4.17%)	4 / 59 (6.78%)	
occurrences (all)	3	4	
Constipation			
subjects affected / exposed	9 / 48 (18.75%)	9 / 59 (15.25%)	
occurrences (all)	14	11	
Diarrhoea			

subjects affected / exposed	18 / 48 (37.50%)	18 / 59 (30.51%)	
occurrences (all)	23	23	
Dry mouth			
subjects affected / exposed	4 / 48 (8.33%)	1 / 59 (1.69%)	
occurrences (all)	4	1	
Dyspepsia			
subjects affected / exposed	1 / 48 (2.08%)	3 / 59 (5.08%)	
occurrences (all)	1	4	
Nausea			
subjects affected / exposed	15 / 48 (31.25%)	20 / 59 (33.90%)	
occurrences (all)	26	47	
Stomatitis			
subjects affected / exposed	3 / 48 (6.25%)	2 / 59 (3.39%)	
occurrences (all)	4	2	
Toothache			
subjects affected / exposed	0 / 48 (0.00%)	3 / 59 (5.08%)	
occurrences (all)	0	3	
Vomiting			
subjects affected / exposed	9 / 48 (18.75%)	8 / 59 (13.56%)	
occurrences (all)	11	13	
Skin and subcutaneous tissue disorders			
Ecchymosis			
subjects affected / exposed	1 / 48 (2.08%)	4 / 59 (6.78%)	
occurrences (all)	1	4	
Erythema			
subjects affected / exposed	1 / 48 (2.08%)	5 / 59 (8.47%)	
occurrences (all)	9	5	
Hyperhidrosis			
subjects affected / exposed	2 / 48 (4.17%)	4 / 59 (6.78%)	
occurrences (all)	3	4	
Night sweats			
subjects affected / exposed	4 / 48 (8.33%)	4 / 59 (6.78%)	
occurrences (all)	4	4	
Pruritus			
subjects affected / exposed	6 / 48 (12.50%)	8 / 59 (13.56%)	
occurrences (all)	6	8	

Pruritus generalised subjects affected / exposed occurrences (all)	6 / 48 (12.50%) 9	2 / 59 (3.39%) 2	
Rash subjects affected / exposed occurrences (all)	3 / 48 (6.25%) 4	5 / 59 (8.47%) 8	
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	5 / 48 (10.42%) 8	7 / 59 (11.86%) 8	
Back pain subjects affected / exposed occurrences (all)	5 / 48 (10.42%) 6	6 / 59 (10.17%) 8	
Bone pain subjects affected / exposed occurrences (all)	4 / 48 (8.33%) 5	5 / 59 (8.47%) 5	
Muscle spasms subjects affected / exposed occurrences (all)	6 / 48 (12.50%) 6	6 / 59 (10.17%) 7	
Musculoskeletal pain subjects affected / exposed occurrences (all)	4 / 48 (8.33%) 4	7 / 59 (11.86%) 9	
Myalgia subjects affected / exposed occurrences (all)	3 / 48 (6.25%) 4	1 / 59 (1.69%) 1	
Pain in extremity subjects affected / exposed occurrences (all)	5 / 48 (10.42%) 9	5 / 59 (8.47%) 5	
Infections and infestations			
Nasopharyngitis subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	6 / 59 (10.17%) 7	
Rhinovirus infection subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	3 / 59 (5.08%) 4	
Upper respiratory tract infection			

subjects affected / exposed occurrences (all)	3 / 48 (6.25%) 5	9 / 59 (15.25%) 14	
Urinary tract infection subjects affected / exposed occurrences (all)	2 / 48 (4.17%) 3	5 / 59 (8.47%) 5	
Metabolism and nutrition disorders			
Decreased appetite subjects affected / exposed occurrences (all)	7 / 48 (14.58%) 7	10 / 59 (16.95%) 13	
Gout subjects affected / exposed occurrences (all)	2 / 48 (4.17%) 2	5 / 59 (8.47%) 9	
Hyperkalaemia subjects affected / exposed occurrences (all)	2 / 48 (4.17%) 3	4 / 59 (6.78%) 9	
Hyperuricaemia subjects affected / exposed occurrences (all)	3 / 48 (6.25%) 5	4 / 59 (6.78%) 5	
Hypocalcaemia subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	4 / 59 (6.78%) 7	
Hypokalaemia subjects affected / exposed occurrences (all)	3 / 48 (6.25%) 7	0 / 59 (0.00%) 0	
Hyponatraemia subjects affected / exposed occurrences (all)	3 / 48 (6.25%) 8	2 / 59 (3.39%) 2	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 November 2015	This amendment included revisions to study eligibility criteria based on feedback from investigators and discussion with the independent Hepatic Expert Committee and clarified some aspects of study conduct.
29 September 2016	Following the first interim review, this amendment was implemented to suspend enrollment of new subjects into the 9.4 mg/kg arm and permanently close enrollment into the 4.7 mg/kg arm. The study was unblinded and randomization was discontinued. This amendment added a second planned interim review with guidelines for interpretation of results.
13 March 2018	This amendment confirmed the final study analysis would occur per protocol 18 months after the last subject had been enrolled because sufficient data had been collected. The study was closed to further subject enrollment. An Extension Phase was added to the protocol to allow continued treatment for subjects benefiting from treatment with study drug and to continue collection of survival data for subjects no longer receiving treatment.
20 December 2018	This amendment extended the Extension Phase from 1 year to 2 years.

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported