



## Clinical trial results:

### A Phase Ib Study of Eltrombopag and Azacitidine in Patients with High Risk Myelodysplastic Syndromes and Related Disorders

#### Summary

EudraCT number	2013-000341-39
Trial protocol	GB
Global end of trial date	07 September 2020

#### Results information

Result version number	v1 (current)
This version publication date	23 September 2021
First version publication date	23 September 2021
Summary attachment (see zip file)	ELASTIC End of Trial Clinical Trial Summary Report (ELASTIC End of Trial Clinical Trial Summary Report v1.0 07-Sep-2021.docx.pdf)

#### Trial information

##### Trial identification

Sponsor protocol code	RG_12-268
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##### Additional study identifiers

ISRCTN number	ISRCTN05858391
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	University of Birmingham
Sponsor organisation address	Edgbaston, Birmingham, United Kingdom, B15 2TT
Public contact	Sonia Fox, University of Birmingham, +44 01214143289, elastic@trials.bham.ac.uk
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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	26 August 2021
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	07 September 2020
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the safety and tolerability of eltrombopag (an oral thrombopoietin receptor agonist) in combination with azacitidine (the standard therapy) in patients with advanced myelodysplastic syndromes and related diseases by establishing the Maximum Tolerated Dose (MTD) and Optimum Biological Dose (OBD).

Protection of trial subjects:

The Independent Safety Monitoring Committee (ISMC) met after every cohort to evaluate safety data and consider if the next cohort should be opened.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 July 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 31
Worldwide total number of subjects	31
EEA total number of subjects	0

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)	0
From 65 to 84 years	25
85 years and over	6

## Subject disposition

### Recruitment

Recruitment details:

This trial recruited patients with IPSS INT-2/high-risk Myelodysplastic Syndromes (MDS), Chronic Myelomonocytic Leukaemia (CMML-2) and Acute Myeloid Leukaemia (AML) with less than 30% blasts.

### Pre-assignment

Screening details:

The following tests were performed during screening to ensure the patient was eligible and fit enough to participate in the trial: physical exam (including height, weight, blood pressure and spleen measurement), blood tests, ECG and a pregnancy test (if appropriate).

### Period 1

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

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Cohort 1 (25mg eltrombopag)

Arm description:

Patients in this cohort received eltrombopag at their allocated dose (25mg) from day 1 (i.e. a week before cycle 1 of azacitidine) and continuously through the first two azacitidine cycles (each of 4 weeks duration). Patients were then given a third cycle of azacitidine alone to allow a period of 'wash-out' prior to bone marrow assessment. The dose of azacitidine was 75mg/m<sup>2</sup> daily sub-cutaneous for 7 days (5 days on, 2 days off, 2 days on schedule).

Arm type	cohort
Investigational medicinal product name	eltrombopag
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients received eltrombopag at their allocated dose (see below) from day 1 (i.e. a week before cycle 1 of azacitidine) and continuously through the first two azacitidine cycles, each of 4 weeks duration (with pre-defined delays up to a total of 6 weeks duration per cycle).

Cohort 1: 25mg OD

Cohort 2: 50mg OD

Cohort 3: 100mg OD

Cohort 4: 200mg OD

Cohort 5: 300mg OD

Patients were then given a third cycle of azacitidine alone to allow a period of 'wash-out' prior to bone marrow assessment.

Investigational medicinal product name	azacitidine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for cutaneous solution
Routes of administration	Subcutaneous use

Dosage and administration details:

Patients received a minimum of 3 cycles of azacitidine, starting at week 2 (day 8). Patients could receive up to 6 cycles of azacitidine whilst on trial. Treatment with azacitidine was continued as long as the patient continued to benefit or until disease progression as per its licences, at the discretion of the treating clinician. The dose of azacitidine was 75mg/m<sup>2</sup> daily sub-cutaneous for 7 days (5 days on, 2 days off, 2 days on schedule).

<b>Arm title</b>	Cohort 2 (50mg eltrombopag)
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**Arm description:**

Patients in this cohort received eltrombopag at their allocated dose (50mg) from day 1 (i.e. a week before cycle 1 of azacitidine) and continuously through the first two azacitidine cycles (each of 4 weeks duration). Patients were then given a third cycle of azacitidine alone to allow a period of 'wash-out' prior to bone marrow assessment. The dose of azacitidine was 75mg/m<sup>2</sup> daily sub-cutaneous for 7 days (5 days on, 2 days off, 2 days on schedule)

Arm type	cohort
Investigational medicinal product name	eltrombopag
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

**Dosage and administration details:**

Patients received eltrombopag at their allocated dose (see below) from day 1 (i.e. a week before cycle 1 of azacitidine) and continuously through the first two azacitidine cycles, each of 4 weeks duration (with pre-defined delays up to a total of 6 weeks duration per cycle).

Cohort 1: 25mg OD

Cohort 2: 50mg OD

Cohort 3: 100mg OD

Cohort 4: 200mg OD

Cohort 5: 300mg OD

Patients were then given a third cycle of azacitidine alone to allow a period of 'wash-out' prior to bone marrow assessment.

Investigational medicinal product name	azacitidine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for cutaneous solution
Routes of administration	Subcutaneous use

**Dosage and administration details:**

Patients received a minimum of 3 cycles of azacitidine, starting at week 2 (day 8). Patients could receive up to 6 cycles of azacitidine whilst on trial. Treatment with azacitidine was continued as long as the patient continued to benefit or until disease progression as per its licences, at the discretion of the treating clinician. The dose of azacitidine was 75mg/m<sup>2</sup> daily sub-cutaneous for 7 days (5 days on, 2 days off, 2 days on schedule).

<b>Arm title</b>	Cohort 3 (100mg eltrombopag)
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**Arm description:**

Patients in this cohort received eltrombopag at their allocated dose (100mg) from day 1 (i.e. a week before cycle 1 of azacitidine) and continuously through the first two azacitidine cycles (each of 4 weeks duration). Patients were then given a third cycle of azacitidine alone to allow a period of 'wash-out' prior to bone marrow assessment. The dose of azacitidine was 75mg/m<sup>2</sup> daily sub-cutaneous for 7 days (5 days on, 2 days off, 2 days on schedule)

Arm type	cohort
Investigational medicinal product name	azacitidine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for cutaneous solution
Routes of administration	Subcutaneous use

**Dosage and administration details:**

Patients received a minimum of 3 cycles of azacitidine, starting at week 2 (day 8). Patients could receive up to 6 cycles of azacitidine whilst on trial. Treatment with azacitidine was continued as long as the patient continued to benefit or until disease progression as per its licences, at the discretion of the treating clinician. The dose of azacitidine was 75mg/m<sup>2</sup> daily sub-cutaneous for 7 days (5 days on, 2 days off, 2 days on schedule).

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

**Dosage and administration details:**

Patients received eltrombopag at their allocated dose (see below) from day 1 (i.e. a week before cycle 1 of azacitidine) and continuously through the first two azacitidine cycles, each of 4 weeks duration (with pre-defined delays up to a total of 6 weeks duration per cycle).

Cohort 1: 25mg OD

Cohort 2: 50mg OD

Cohort 3: 100mg OD

Cohort 4: 200mg OD

Cohort 5: 300mg OD

Patients were then given a third cycle of azacitidine alone to allow a period of 'wash-out' prior to bone marrow assessment.

<b>Arm title</b>	Cohort 4 (200mg eltrombopag)
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**Arm description:**

Patients in this cohort received eltrombopag at their allocated dose (200mg) from day 1 (i.e. a week before cycle 1 of azacitidine) and continuously through the first two azacitidine cycles (each of 4 weeks duration). Patients were then given a third cycle of azacitidine alone to allow a period of 'wash-out' prior to bone marrow assessment. The dose of azacitidine was 75mg/m<sup>2</sup> daily sub-cutaneous for 7 days (5 days on, 2 days off, 2 days on schedule)

Arm type	cohort
Investigational medicinal product name	eltrombopag
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

**Dosage and administration details:**

Patients received eltrombopag at their allocated dose (see below) from day 1 (i.e. a week before cycle 1 of azacitidine) and continuously through the first two azacitidine cycles, each of 4 weeks duration (with pre-defined delays up to a total of 6 weeks duration per cycle).

Cohort 1: 25mg OD

Cohort 2: 50mg OD

Cohort 3: 100mg OD

Cohort 4: 200mg OD

Cohort 5: 300mg OD

Patients were then given a third cycle of azacitidine alone to allow a period of 'wash-out' prior to bone marrow assessment.

Investigational medicinal product name	azacitidine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for cutaneous solution
Routes of administration	Subcutaneous use

**Dosage and administration details:**

Patients received a minimum of 3 cycles of azacitidine, starting at week 2 (day 8). Patients could receive up to 6 cycles of azacitidine whilst on trial. Treatment with azacitidine was continued as long as the patient continued to benefit or until disease progression as per its licences, at the discretion of the treating clinician. The dose of azacitidine was 75mg/m<sup>2</sup> daily sub-cutaneous for 7 days (5 days on, 2 days off, 2 days on schedule).

<b>Arm title</b>	Cohort 5 (300mg eltrombopag)
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**Arm description:**

Patients in this cohort received eltrombopag at their allocated dose (300mg) from day 1 (i.e. a week before cycle 1 of azacitidine) and continuously through the first two azacitidine cycles (each of 4 weeks duration). Patients were then given a third cycle of azacitidine alone to allow a period of 'wash-out' prior to bone marrow assessment. The dose of azacitidine was 75mg/m<sup>2</sup> daily sub-cutaneous for 7 days (5 days on, 2 days off, 2 days on schedule)

Arm type	cohort
Investigational medicinal product name	eltrombopag
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

**Dosage and administration details:**

Patients received eltrombopag at their allocated dose (see below) from day 1 (i.e. a week before cycle 1 of azacitidine) and continuously through the first two azacitidine cycles, each of 4 weeks duration (with pre-defined delays up to a total of 6 weeks duration per cycle).

Cohort 1: 25mg OD

Cohort 2: 50mg OD

Cohort 3: 100mg OD

Cohort 4: 200mg OD

Cohort 5: 300mg OD

Patients were then given a third cycle of azacitidine alone to allow a period of 'wash-out' prior to bone marrow assessment.

Investigational medicinal product name	azacitidine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for cutaneous solution
Routes of administration	Subcutaneous use

**Dosage and administration details:**

Patients received a minimum of 3 cycles of azacitidine, starting at week 2 (day 8). Patients could receive up to 6 cycles of azacitidine whilst on trial. Treatment with azacitidine was continued as long as the patient continued to benefit or until disease progression as per its licences, at the discretion of the treating clinician. The dose of azacitidine was 75mg/m<sup>2</sup> daily sub-cutaneous for 7 days (5 days on, 2 days off, 2 days on schedule).

<b>Number of subjects in period 1</b>	Cohort 1 (25mg eltrombopag)	Cohort 2 (50mg eltrombopag)	Cohort 3 (100mg eltrombopag)
Started	5	3	4
Completed	1	2	3
Not completed	4	1	1
Adverse event, serious fatal	-	-	-
Treatment discontinuation	-	-	1
Disease progression	-	-	-
Toxicity	2	-	-
Died	2	1	-
Other toxicity	-	-	-

<b>Number of subjects in period 1</b>	Cohort 4 (200mg eltrombopag)	Cohort 5 (300mg eltrombopag)
Started	4	15
Completed	2	9
Not completed	2	6
Adverse event, serious fatal	-	1
Treatment discontinuation	-	-
Disease progression	-	1
Toxicity	-	-
Died	2	1
Other toxicity	-	3



## Baseline characteristics

### Reporting groups

Reporting group title	Cohort 1 (25mg eltrombopag)
Reporting group description:	
Patients in this cohort received eltrombopag at their allocated dose (25mg) from day 1 (i.e. a week before cycle 1 of azacitidine) and continuously through the first two azacitidine cycles (each of 4 weeks duration). Patients were then given a third cycle of azacitidine alone to allow a period of 'wash-out' prior to bone marrow assessment. The dose of azacitidine was 75mg/m2 daily sub-cutaneous for 7 days (5 days on, 2 days off, 2 days on schedule).	
Reporting group title	Cohort 2 (50mg eltrombopag)
Reporting group description:	
Patients in this cohort received eltrombopag at their allocated dose (50mg) from day 1 (i.e. a week before cycle 1 of azacitidine) and continuously through the first two azacitidine cycles (each of 4 weeks duration). Patients were then given a third cycle of azacitidine alone to allow a period of 'wash-out' prior to bone marrow assessment. The dose of azacitidine was 75mg/m2 daily sub-cutaneous for 7 days (5 days on, 2 days off, 2 days on schedule).	
Reporting group title	Cohort 3 (100mg eltrombopag)
Reporting group description:	
Patients in this cohort received eltrombopag at their allocated dose (100mg) from day 1 (i.e. a week before cycle 1 of azacitidine) and continuously through the first two azacitidine cycles (each of 4 weeks duration). Patients were then given a third cycle of azacitidine alone to allow a period of 'wash-out' prior to bone marrow assessment. The dose of azacitidine was 75mg/m2 daily sub-cutaneous for 7 days (5 days on, 2 days off, 2 days on schedule).	
Reporting group title	Cohort 4 (200mg eltrombopag)
Reporting group description:	
Patients in this cohort received eltrombopag at their allocated dose (200mg) from day 1 (i.e. a week before cycle 1 of azacitidine) and continuously through the first two azacitidine cycles (each of 4 weeks duration). Patients were then given a third cycle of azacitidine alone to allow a period of 'wash-out' prior to bone marrow assessment. The dose of azacitidine was 75mg/m2 daily sub-cutaneous for 7 days (5 days on, 2 days off, 2 days on schedule).	
Reporting group title	Cohort 5 (300mg eltrombopag)
Reporting group description:	
Patients in this cohort received eltrombopag at their allocated dose (300mg) from day 1 (i.e. a week before cycle 1 of azacitidine) and continuously through the first two azacitidine cycles (each of 4 weeks duration). Patients were then given a third cycle of azacitidine alone to allow a period of 'wash-out' prior to bone marrow assessment. The dose of azacitidine was 75mg/m2 daily sub-cutaneous for 7 days (5 days on, 2 days off, 2 days on schedule).	

Reporting group values	Cohort 1 (25mg eltrombopag)	Cohort 2 (50mg eltrombopag)	Cohort 3 (100mg eltrombopag)
Number of subjects	5	3	4
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			



Age continuous Units: years median full range (min-max)	74 73 to 76	80 62 to 81	72.5 71 to 81
Gender categorical Units: Subjects			
Female	1	1	1
Male	4	2	3
ECOG Performance Status Units: Subjects			
PS 0	2	3	3
PS 1	2	0	1
Not known	0	0	0
Missing	1	0	0
Spleen Assessment Units: Subjects			
Palpable	1	0	1
Not palpable	4	3	3
Not known	0	0	0
Not performed	0	0	0
Missing	0	0	0
Bone Marrow Cellularity Units: Subjects			
Hypocellular	0	2	1
Normal	0	0	2
Hypercellular	3	1	1
N/A	2	0	0
Missing	0	0	0
Bone marrow fibrosis grade Units: Subjects			
Grade 1	2	1	1
Grade 2	0	0	1
Grade 3	0	0	0
Grade 4	0	0	0
Missing	3	2	2
Karyotype Units: Subjects			
14/20 cells examined showed an abnormal hyperdiplo	0	0	0
43, XY-5add(6)(q13)-7-18-21+Mar (6)45,X,-Y(24)	0	0	0
44, XY, -5, -7, +8, -2, add (17)(p13), add(19)(q1	0	0	0
44 45, XX, -4, -5, -6, -9, add (11)(p?), +2mar, i	1	0	0
45, XY, -7 [3]/45, XY, del (12)(p12PB)[7]/46,XY [	0	0	1
45, XY, inv [3] (q21q 26-2), -7[10]	0	0	0
45,XY-7[4] / 46,XY[16] - total 20 examined	0	0	0
46 X,Y in 32 cells (Normal)	0	0	0
46 XY (Normal Karyotype)	0	0	1
46, XX, inv (2) (p13q35), r (11)(p13q13) [18]/47,	0	0	0

46, XX[20]	0	0	0
46, XY, add (5)(p15), del (5) (q1? 3q33), -12+mar [	1	0	0
46XY	0	0	0
47, XY, +8[16]/47, XY, del(7) (q22q34),+8[4]	0	0	0
47, xx, +8, del(12) (p11.2) [7] / 46, xx [3]	0	0	0
47xx, +8[9]/46,xx	0	0	0
48, XY, +8 [3] / 46, XY [17]	0	0	0
5q31 and 7q31 deletions detected	0	0	0
Abnormal karotype with del (20q)	1	0	0
Abnormal karyotype including del (5q)	0	0	0
Abnormal karyotype with del (6q) and monosomy 7 45	0	1	0
Complex/monosomal karotype	0	0	0
Failed	1	0	0
Missing	0	0	0
Normal	0	1	1
Normal karyotope	0	1	0
Normal karyotope 46, xY [20]	0	0	1
Not known	1	0	0
Number of transfusions per patient Units: Subjects			
0 transfusions	3	1	2
1 transfusion	0	0	0
2 transfusions	1	1	1
3 transfusions	0	1	1
4 transfusions	0	0	0
5 transfusions	1	0	0
8 transfusions	0	0	0
Disease Type Units: Subjects			
AML	2	0	1
INT 2 MDS	1	3	2
High risk MDS	1	0	1
CMML-2	1	0	0
Missing	0	0	0
WHO Disease classification Units: Subjects			
Refractory anaemia with excess blasts 1-RAEB (1)	1	1	1
Refractory anaemia with excess blasts 2-RAEB (2)	0	2	1
Refractory cytopenia with multilineage dysplasia - CMML (2)	0	0	1
Myelodysplastic/myeloproliferative disorder, uncla	1	0	0
AML with myelodysplasia	0	0	0
Missing	3	0	1
	0	0	0

Prothrombin Time Units: Seconds median full range (min-max)	11.9 11.3 to 13.8	11.8 10.4 to 13.0	11.9 1.0 to 12.3
Activated partial thromboplastin time (APPT) Units: seconds median full range (min-max)	31.6 22.8 to 35.9	32.7 27.2 to 48.4	26.1 0.9 to 32.6
Fibrinogen Units: mg/dL median full range (min-max)	3.7 3.5 to 4.1	2.8 2.8 to 2.8	0 0 to 0
D-dimer Units: ng/mL median full range (min-max)	504.0 142.0 to 9999.0	627.0 284.0 to 2570.0	383.0 383.0 to 383.0
Fibrin degradation products (FDP) Units: mg/L median full range (min-max)	2.2 2.2 to 2.2	0 0 to 0	0 0 to 0
Systolic blood pressure Units: mm Hg median full range (min-max)	123.5 118.0 to 153.0	143.0 104.0 to 145.0	129.0 105.0 to 148.0
Diastolic blood pressure Units: mm Hg median full range (min-max)	63.0 56.0 to 76.0	63.0 61.0 to 70.0	64.0 57.0 to 72.0
Pulse Units: bpm median full range (min-max)	76.5 66.0 to 89.0	70.0 42.0 to 84.0	66.5 54.0 to 80.0
Height Units: meters median full range (min-max)	1.7 1.6 to 1.8	1.6 1.5 to 1.7	1.7 1.6 to 1.8
Weight Units: kg median full range (min-max)	73.5 58.2 to 106.2	55.0 52.6 to 82.3	78.6 70.4 to 90.1
Body surface area (BSA) Units: m2 median full range (min-max)	1.9 1.6 to 2.3	1.6 1.5 to 1.9	1.9 1.3 to 2.1
Spleen size Units: cm (largest diameter) median full range (min-max)	0.0 0.0 to 0.0	0.0 0.0 to 0.0	0.0 0.0 to 0.1
Neutrophils Units: Percentage median	2.8	12.0	47.6

full range (min-max)	2.8 to 2.8	12.0 to 12.0	31.8 to 63.4
Lymphocytes			
Units: Percentage			
median	2.3	52.0	26.7
full range (min-max)	2.3 to 2.3	52.0 to 52.0	17.1 to 36.4
Metamyelocytes			
Units: Percentage			
median	2.8	2.0	0
full range (min-max)	2.8 to 2.8	2.0 to 2.0	0.0 to 0.0
Myelocytes			
Units: Percentage			
median	0.9	9.0	0
full range (min-max)	0.9 to 0.9	9.0 to 9.0	0 to 0.0
Promyelocytes			
Units: Percentage			
median	0.6	0	0
full range (min-max)	0.6 to 0.6	0 to 0	0 to 0
Monocytes			
Units: Percentage			
median	0.2	23.0	23.2
full range (min-max)	0.2 to 0.2	23.0 to 23.0	14.6 to 31.8
Eosinophils			
Units: Percentage			
median	0.0	0	2.1
full range (min-max)	0.0 to 0.0	0 to 0	1.8 to 2.4
Basophils			
Units: Percentage			
median	0.0	0	0.0
full range (min-max)	0.0 to 0.0	0 to 0	0.0 to 0.0
Blasts			
Units: Percentage			
median	1.0	1.0	0.0
full range (min-max)	1.0 to 1.0	0.0 to 2.0	0.0 to 0.0
Nucleated red blood cells			
Units: Percentage			
median	0	0	0
full range (min-max)	0 to 0	0 to 0	
Haemoglobin			
Units: g/L			
median	97.0	103.0	109.5
full range (min-max)	74.0 to 111.0	100.0 to 118.0	85.0 to 117.0
Platelets			
Units: 109/L			
median	14.0	19.0	40.0
full range (min-max)	9.0 to 57.0	18.0 to 72.0	27.0 to 72.0
Mean cell volume			
Units: fL			
median	91.0	100.0	98.5
full range (min-max)	87.0 to 101.0	97.0 to 112.0	87.0 to 116.0
Mean cell haemoglobin			
Units: pg			
median	29.6	33.2	33.3

full range (min-max)	29.3 to 36.3	29.7 to 40.6	29.4 to 38.6
White blood cell count			
Units: 109/L			
median	2.8	3.2	2.8
full range (min-max)	0.9 to 9.6	1.7 to 3.6	1.1 to 82.2
Neutrophils (ANC)			
Units: 109/L			
median	0.8	1.2	0.6
full range (min-max)	0.0 to 2.7	0.8 to 1.5	0.3 to 2.6
Lymphocytes			
Units: 109/L			
median	1.5	1.5	0.7
full range (min-max)	0.6 to 2.3	0.8 to 1.8	0.7 to 0.8
Monocytes			
Units: 109/L			
median	0.1	0.1	0.3
full range (min-max)	0.0 to 0.2	0.0 to 0.6	0.0 to 0.7
Eosinophils			
Units: 109/L			
median	0.0	0.0	0.0
full range (min-max)	0.0 to 0.0	0.0 to 0.0	0.0 to 0.1
Basophils			
Units: 109/L			
median	0.0	0.0	0.0
full range (min-max)	0.0 to 0.0	0.0 to 0.0	0.0 to 0.0
Blasts (peripheral blood)			
Units: Percentage			
median	0.5	0.0	0
full range (min-max)	0.0 to 1.0	0.0 to 0.0	0.0 to 0.0
Morphology			
Morphology blasts			
Units: Percentage			
median	21.0	10.5	8.0
full range (min-max)	12.0 to 26.0	8.0 to 13.0	4.0 to 21.0
Immunophenotyping			
Baseline blasts			
Units: Percentage			
median	6.5	11.0	3.0
full range (min-max)	5.0 to 23.0	6.0 to 11.0	3.0 to 3.0
Trephine			
baseline blasts			
Units: Percentage			
median	20.0	5.0	10.0
full range (min-max)	20.0 to 20.0	5.0 to 5.0	5.0 to 15.0
Time from diagnosis			
Units: days			
median	17	56	36
full range (min-max)	0.0 to 47.0	30 to 808	23 to 49
<b>Reporting group values</b>	Cohort 4 (200mg eltrombopag)	Cohort 5 (300mg eltrombopag)	Total
Number of subjects	4	15	31

Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
median	69.5	75	
full range (min-max)	63 to 79	62 to 86	-
Gender categorical Units: Subjects			
Female	1	5	9
Male	3	10	22
ECOG Performance Status Units: Subjects			
PS 0	2	4	14
PS 1	2	6	11
Not known	0	4	4
Missing	0	1	2
Spleen Assessment Units: Subjects			
Palpable	0	0	2
Not palpable	2	10	22
Not known	0	3	3
Not performed	2	1	3
Missing	0	1	1
Bone Marrow Cellularity Units: Subjects			
Hypocellular	2	3	8
Normal	0	2	4
Hypercellular	2	9	16
N/A	0	0	2
Missing	0	1	1
Bone marrow fibrosis grade Units: Subjects			
Grade 1	1	6	11
Grade 2	0	1	2
Grade 3	0	1	1
Grade 4	1	0	1
Missing	2	7	16
Karyotype Units: Subjects			
14/20 cells examined showed an abnormal hyperdiplo	0	1	1

43, XY-5add(6)(q13)-7-18-21+Mar (6)45,X,-Y(24)	0	1	1
44, XY, -5, -7, +8, -2, add (17)(p1? 3), add(19)(q1	0	1	1
44 45, XX, -4, -5, -6, -9, add (11) (p?), +2mar, i	0	0	1
45, XY, -7 [3]/45, XY, del (12) (p12PB)[7]/46,XY [	0	0	1
45, XY, inv [3] (q21q 26-2), -7[10]	0	1	1
45,XY-7[4] / 46,XY[16] - total 20 examined	0	1	1
46 X,Y in 32 cells (Normal)	1	0	1
46 XY (Normal Karyotype)	0	0	1
46, XX, inv (2) (p13q35), r (11) (p13q13) [18]/47,	0	1	1
46, XX[20]	0	1	1
46, XY, add (5)(p15), del (5) (q1? 3q33), -12+mar [	0	0	1
46XY	1	0	1
47, XY, +8[16]/47, XY, del(7) (q22q34),+8[4]	0	1	1
47, xx, +8, del(12) (p11.2) [7] / 46, xx [3]	0	1	1
47xx, +8[9]/46,xx	0	1	1
48, XY, +8 [3] / 46, XY [17]	0	1	1
5q31 and 7q31 deletions detected	1	0	1
Abnormal karotype with del (20q)	0	0	1
Abnormal karyotype including del (5q)	0	1	1
Abnormal karyotype with del (6q) and monosomy 7 45	0	0	1
Complex/monosomal karotype	1	0	1
Failed	0	0	1
Missing	0	1	1
Normal	0	0	2
Normal karyotope	0	1	2
Normal karyotpe 46, xY [20]	0	1	2
Not known	0	0	1
Number of transfusions per patient Units: Subjects			
0 transfusions	2	8	16
1 transfusion	1	2	3
2 transfusions	0	1	4
3 transfusions	1	2	5
4 transfusions	0	1	1
5 transfusions	0	0	1
8 transfusions	0	1	1
Disease Type Units: Subjects			
AML	0	2	5
INT 2 MDS	1	5	12
High risk MDS	3	7	12
CMML-2	0	0	1
Missing	0	1	1
WHO Disease classification			

Units: Subjects			
Refractory anaemia with excess blasts 1-RAEB (1)	2	2	7
Refractory anaemia with excess blasts 2-RAEB (2)	2	6	11
Refractory cytopenia with multilineage dysplasia - CMML (2)	0	3	4
Myelodysplastic/myeloproliferative disorder, uncla	0	0	1
AML with myelodysplasia	0	1	1
Missing	0	2	6
	0	1	1
Prothrombin Time			
Units: Seconds			
median	12.5	13.7	
full range (min-max)	10.3 to 13.0	11.0 to 35.6	-
Activated partial thromboplastin time (APPT)			
Units: seconds			
median	27.6	29.3	
full range (min-max)	25.0 to 34.0	24.5 to 38.1	-
Fibrinogen			
Units: mg/dL			
median	4.0	4.3	
full range (min-max)	2.8 to 6.9	1.4 to 5.0	-
D-dimer			
Units: ng/mL			
median	735.0	285.0	
full range (min-max)	735.0 to 735.0	77.7 to 3183.0	-
Fibrin degradation products (FDP)			
Units: mg/L			
median	0	0	
full range (min-max)	0 to 0	0 to 0	-
Systolic blood pressure			
Units: mm Hg			
median	143.0	122.5	
full range (min-max)	139.0 to 158.0	102.0 to 178.0	-
Diastolic blood pressure			
Units: mm Hg			
median	74.5	72.5	
full range (min-max)	64.0 to 96.0	52.0 to 92.0	-
Pulse			
Units: bpm			
median	80.5	73.0	
full range (min-max)	59.0 to 105.0	56.0 to 90.0	-
Height			
Units: meters			
median	1.7	1.7	
full range (min-max)	1.5 to 1.9	1.2 to 1.8	-
Weight			
Units: kg			
median	90.4	76.3	
full range (min-max)	75.0 to 94.0	36.5 to 131.1	-



Body surface area (BSA) Units: m2 median full range (min-max)	1.9 1.4 to 2.1	1.9 1.5 to 2.2	-
Spleen size Units: cm (largest diameter) median full range (min-max)	0 0.0 to 0.0	0.0 0.0 to 0.0	-
Neutrophils Units: Percentage median full range (min-max)	40.9 34.0 to 629.6	13.0 1.1 to 41.7	-
Lymphocytes Units: Percentage median full range (min-max)	40.9 17.0 to 277.8	35.4 1.1 to 277.8	-
Metamyelocytes Units: Percentage median full range (min-max)	4.0 4.0 to 4.0	0.0 0.0 to 0.0	-
Myelocytes Units: Percentage median full range (min-max)	4.0 4.0 to 4.0	0.0 0.0 to 4.0	-
Promyelocytes Units: Percentage median full range (min-max)	2.0 2.0 to 2.0	0.0 0.0 to 0.0	-
Monocytes Units: Percentage median full range (min-max)	13.0 4.5 to 37.0	4.0 0.1 to 20.8	-
Eosinophils Units: Percentage median full range (min-max)	1.9 1.0 to 4.5	0.2 0.0 to 1.3	-
Basophils Units: Percentage median full range (min-max)	1.0 0.0 to 7.4	0.0 0.0 to 0.0	-
Blasts Units: Percentage median full range (min-max)	2.0 2.0 to 2.0	0.0 0.0 to 42.0	-
Nucleated red blood cells Units: Percentage median full range (min-max)	20.0 20.0 to 20.0	0.0 0.0 to 0.0	-
Haemoglobin Units: g/L median full range (min-max)	94.0 80.0 to 119.0	100.5 80.0 to 122.0	-

Platelets Units: 109/L median full range (min-max)	32.5 12.0 to 118.0	37.0 13.0 to 88.0	-
Mean cell volume Units: fL median full range (min-max)	96.0 74.0 to 108.0	95.0 80.0 to 111.0	-
Mean cell haemoglobin Units: pg median full range (min-max)	31.6 22.6 to 36.0	31.6 26.9 to 37.8	-
White blood cell count Units: 109/L median full range (min-max)	3.8 1.7 to 10.1	2.9 1.1 to 6.7	-
Neutrophils (ANC) Units: 109/L median full range (min-max)	2.1 0.7 to 5.6	0.5 0.2 to 2.8	-
Lymphocytes Units: 109/L median full range (min-max)	1.3 0.9 to 1.9	1.4 0.4 to 3.0	-
Monocytes Units: 109/L median full range (min-max)	0.1 0.1 to 0.3	0.1 0.1 to 1.0	-
Eosinophils Units: 109/L median full range (min-max)	0.0 0.0 to 0.3	0.0 0.0 to 0.8	-
Basophils Units: 109/L median full range (min-max)	0.0 0.0 to 0.8	0.0 0.0 to 0.1	-
Blasts (peripheral blood) Units: Percentage median full range (min-max)	0.0 0.0 to 0.0	6.0 0.0 to 42.0	-
Morphology			
Morphology blasts			
Units: Percentage median full range (min-max)	6.5 2.0 to 19.0	14.0 3.0 to 47.0	-
Immunophenotyping			
Baseline blasts			
Units: Percentage median full range (min-max)	26.0 26.0 to 26.0	10.5 0.00 to 18.0	-
Trephine			
baseline blasts			

Units: Percentage			
median	0	13.0	
full range (min-max)	0 to 0	5.0 to 20.0	-
Time from diagnosis			
Units: days			
median	31	49	
full range (min-max)	10 to 3137	9 to 1645	-

## End points

### End points reporting groups

Reporting group title	Cohort 1 (25mg eltrombopag)
Reporting group description: Patients in this cohort received eltrombopag at their allocated dose (25mg) from day 1 (i.e. a week before cycle 1 of azacitidine) and continuously through the first two azacitidine cycles (each of 4 weeks duration). Patients were then given a third cycle of azacitidine alone to allow a period of 'wash-out' prior to bone marrow assessment. The dose of azacitidine was 75mg/m <sup>2</sup> daily sub-cutaneous for 7 days (5 days on, 2 days off, 2 days on schedule).	
Reporting group title	Cohort 2 (50mg eltrombopag)
Reporting group description: Patients in this cohort received eltrombopag at their allocated dose (50mg) from day 1 (i.e. a week before cycle 1 of azacitidine) and continuously through the first two azacitidine cycles (each of 4 weeks duration). Patients were then given a third cycle of azacitidine alone to allow a period of 'wash-out' prior to bone marrow assessment. The dose of azacitidine was 75mg/m <sup>2</sup> daily sub-cutaneous for 7 days (5 days on, 2 days off, 2 days on schedule).	
Reporting group title	Cohort 3 (100mg eltrombopag)
Reporting group description: Patients in this cohort received eltrombopag at their allocated dose (100mg) from day 1 (i.e. a week before cycle 1 of azacitidine) and continuously through the first two azacitidine cycles (each of 4 weeks duration). Patients were then given a third cycle of azacitidine alone to allow a period of 'wash-out' prior to bone marrow assessment. The dose of azacitidine was 75mg/m <sup>2</sup> daily sub-cutaneous for 7 days (5 days on, 2 days off, 2 days on schedule).	
Reporting group title	Cohort 4 (200mg eltrombopag)
Reporting group description: Patients in this cohort received eltrombopag at their allocated dose (200mg) from day 1 (i.e. a week before cycle 1 of azacitidine) and continuously through the first two azacitidine cycles (each of 4 weeks duration). Patients were then given a third cycle of azacitidine alone to allow a period of 'wash-out' prior to bone marrow assessment. The dose of azacitidine was 75mg/m <sup>2</sup> daily sub-cutaneous for 7 days (5 days on, 2 days off, 2 days on schedule).	
Reporting group title	Cohort 5 (300mg eltrombopag)
Reporting group description: Patients in this cohort received eltrombopag at their allocated dose (300mg) from day 1 (i.e. a week before cycle 1 of azacitidine) and continuously through the first two azacitidine cycles (each of 4 weeks duration). Patients were then given a third cycle of azacitidine alone to allow a period of 'wash-out' prior to bone marrow assessment. The dose of azacitidine was 75mg/m <sup>2</sup> daily sub-cutaneous for 7 days (5 days on, 2 days off, 2 days on schedule).	

### Primary: Number of Patients Experiencing a Dose Limiting Toxicity

End point title	Number of Patients Experiencing a Dose Limiting Toxicity <sup>[1]</sup>
End point description: A DLT was defined by the following safety and tolerability parameters assessed using the NCI CTC Criteria v4: Progression of disease was not considered a DLT. However, a number of studies in this patient population have described disease progression in patients receiving TpoR agonists. In some cases there were transient blast percentage rises whilst in others there was true disease progression. The precise role of TpoR agonists in this is unclear. An AE deemed to be unrelated to Eltrombopag was not considered a DLT.	
End point type	Primary
End point timeframe: Dose limiting toxicity (DLT) was defined by safety and tolerability parameters within 5 weeks (1 cycle of treatment).	

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 protocol states all analyses will be descriptive. The primary outcome is the number of patients experiencing a dose limiting toxicity according to the protocol definition. This does not require formal statistical analysis.

End point values	Cohort 1 (25mg eltrombopag)	Cohort 2 (50mg eltrombopag)	Cohort 3 (100mg eltrombopag)	Cohort 4 (200mg eltrombopag)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	3	3
Units: patients	0	0	0	0

End point values	Cohort 5 (300mg eltrombopag)			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: patients	0			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Optimal Biological Dose

End point title	Optimal Biological Dose
End point description:	
The Optimal Biological dose (OBD) of eltrombopag in combination with azacitidine was defined as the dose of eltrombopag, provided this is the MTD or less, which maintains a platelet count within the range 100-250 x 10 <sup>9</sup> /L immediately prior to azacitidine treatment. The number of patients that met the OBD definition for at least one time point is reported.	
End point type	Secondary
End point timeframe:	
from the date at which patients began treatment until the date they stopped trial treatment.	

End point values	Cohort 1 (25mg eltrombopag)	Cohort 2 (50mg eltrombopag)	Cohort 3 (100mg eltrombopag)	Cohort 4 (200mg eltrombopag)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	3	4	4
Units: Number of patients	0	1	3	1

End point values	Cohort 5 (300mg)			
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	eltrombopag)			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: Number of patients	5			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Platelet Response (SPC criteria) at Cycle 1

End point title	Platelet Response (SPC criteria) at Cycle 1
End point description:	
After cycles 1 and 2 of Azacitidine, response will be defined by the recovery of platelet count to nadir platelet count + (0.5 x [baseline count – nadir count]). Non- response will be defined as the failure to achieve this. Number of patients with a platelet response after cycle 1 is reported.	
End point type	Secondary
End point timeframe:	
Platelet response was determined after completion of Cycle 1	

End point values	Cohort 1 (25mg eltrombopag)	Cohort 2 (50mg eltrombopag)	Cohort 3 (100mg eltrombopag)	Cohort 4 (200mg eltrombopag)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	3	4	4
Units: patients	2	3	3	3

End point values	Cohort 5 (300mg eltrombopag)			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: patients	11			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Platelet Response (SPC criteria) at Cycle 2

End point title	Platelet Response (SPC criteria) at Cycle 2
End point description:	
After cycles 1 and 2 of Azacitidine, response will be defined by the recovery of platelet count to nadir platelet count + (0.5 x [baseline count – nadir count]). Non- response will be defined as the failure to achieve this. Number of patients with a platelet response after cycle 2 is reported.	

End point type	Secondary
End point timeframe:	
Platelet response was determined after completion of Cycle 2.	

End point values	Cohort 1 (25mg eltrombopag)	Cohort 2 (50mg eltrombopag)	Cohort 3 (100mg eltrombopag)	Cohort 4 (200mg eltrombopag)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	3	4	4
Units: Number of patients	0	3	3	2

End point values	Cohort 5 (300mg eltrombopag)			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: Number of patients	7			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of units of Platelet Transfusions

End point title	Number of units of Platelet Transfusions
End point description:	
The number of units of platelet transfusions during treatment	
End point type	Secondary
End point timeframe:	
Measured throughout the treatment period for each patient.	

End point values	Cohort 1 (25mg eltrombopag)	Cohort 2 (50mg eltrombopag)	Cohort 3 (100mg eltrombopag)	Cohort 4 (200mg eltrombopag)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	3	4	4
Units: Number				
number (not applicable)	38	2	41	5

End point values	Cohort 5 (300mg eltrombopag)			
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Subject group type	Reporting group			
Number of subjects analysed	15			
Units: Number				
number (not applicable)	84			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of red cell transfusions

End point title	Number of red cell transfusions
End point description: Number of red cell transfusions given to patients within each cohort throughout their treatment.	
End point type	Secondary
End point timeframe: Throughout the treatment period.	

End point values	Cohort 1 (25mg eltrombopag)	Cohort 2 (50mg eltrombopag)	Cohort 3 (100mg eltrombopag)	Cohort 4 (200mg eltrombopag)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	3	4	4
Units: number				
arithmetic mean (full range (min-max))	4.8 (0 to 8)	2.3 (0 to 4)	9.8 (0 to 16)	0.8 (0 to 3)

End point values	Cohort 5 (300mg eltrombopag)			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: number				
arithmetic mean (full range (min-max))	6.2 (0 to 22)			

## Statistical analyses

No statistical analyses for this end point

### Secondary: WHO Bleeding assessments during treatment

End point title	WHO Bleeding assessments during treatment
End point description: Bleeding events measured using the WHO Bleeding Scale during treatment	
End point type	Secondary



End point timeframe:

During the trial

End point values	Cohort 1 (25mg eltrombopag)	Cohort 2 (50mg eltrombopag)	Cohort 3 (100mg eltrombopag)	Cohort 4 (200mg eltrombopag)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	2	2	2
Units: Number				
number (not applicable)				
Event Grade 0	2	10	9	4
Event Grade 1	2	1	3	2
Event Grade 2	0	1	1	0
Event Grade 3	0	0	1	0

End point values	Cohort 5 (300mg eltrombopag)			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: Number				
number (not applicable)				
Event Grade 0	8			
Event Grade 1	1			
Event Grade 2	2			
Event Grade 3	1			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Bone marrow blast percentage - Morphology - Cycle 1

End point title	Bone marrow blast percentage - Morphology - Cycle 1
End point description:	
Morphology percentage blasts	
End point type	Secondary
End point timeframe:	
Cycle 1	

End point values	Cohort 1 (25mg eltrombopag)	Cohort 2 (50mg eltrombopag)	Cohort 3 (100mg eltrombopag)	Cohort 4 (200mg eltrombopag)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	2	4	3
Units: Number				
median (full range (min-max))	26 (5 to 43)	21 (15 to 27)	14 (6 to 88)	13 (9 to 20)

End point values	Cohort 5 (300mg eltrombopag)			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: Number				
median (full range (min-max))	9.5 (0 to 47.0)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Bone marrow blast percentage - Immunophenotyping - Cycle 1

End point title	Bone marrow blast percentage - Immunophenotyping - Cycle 1
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End point description:

End point type	Secondary
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End point timeframe:

Cycle 1

End point values	Cohort 1 (25mg eltrombopag)	Cohort 2 (50mg eltrombopag)	Cohort 3 (100mg eltrombopag)	Cohort 4 (200mg eltrombopag)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	2	2
Units: numbers				
median (full range (min-max))	13 (10 to 15)	18 (12 to 19)	37 (9 to 65)	16 (11 to 21)

End point values	Cohort 5 (300mg eltrombopag)			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: numbers				
median (full range (min-max))	9 (1 to 29)			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Bone marrow blast percentage - Trephine - Cycle 1

End point title	Bone marrow blast percentage - Trephine - Cycle 1
End point description:	Trephine Percentage
End point type	Secondary
End point timeframe:	Cycle 1

End point values	Cohort 1 (25mg eltrombopag)	Cohort 2 (50mg eltrombopag)	Cohort 3 (100mg eltrombopag)	Cohort 4 (200mg eltrombopag)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0 <sup>[2]</sup>	2	3	0 <sup>[3]</sup>
Units: Numbers				
median (full range (min-max))	( to )	14 (10 to 18)	24 (8 to 40)	( to )

Notes:

[2] - Trephine not assessed for any patients in this cohort

[3] - No trephine blasts assessed in cohort 4 at cycle 1

End point values	Cohort 5 (300mg eltrombopag)			
Subject group type	Reporting group			
Number of subjects analysed	4			
Units: Numbers				
median (full range (min-max))	12.5 (10 to 50)			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Haematological improvement

End point title	Haematological improvement
End point description:	Haematological response criteria Based on the CLINICAL APPLICATION AND PROPOSAL FOR MODIFICATION OF THE INTERNATIONAL WORKING GROUP (IWG) RESPONSE CRITERIA IN MYELODYSPLASIA
End point type	Secondary

End point timeframe:

Across all cycles

End point values	Cohort 1 (25mg eltrombopag)	Cohort 2 (50mg eltrombopag)	Cohort 3 (100mg eltrombopag)	Cohort 4 (200mg eltrombopag)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	3	4	4
Units: number of patients				
Erythroid response	0	0	0	0
Platelet Response	0	1	2	1
Neutrophil response	0	1	0	0
Relapse/progression after HI	0	0	1	0

End point values	Cohort 5 (300mg eltrombopag)			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: number of patients				
Erythroid response	1			
Platelet Response	5			
Neutrophil response	1			
Relapse/progression after HI	1			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Achievement of Platelet Response according to IWG Criteria - Cycle 1, week 1

End point title	Achievement of Platelet Response according to IWG Criteria - Cycle 1, week 1
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End point description:

The IWG 2006 criteria. These define platelet response as an absolute increase of  $\geq 30 \times 10^9/L$  for patients starting with  $> 20 \times 10^9/L$  platelets or increase from baseline  $< 20 \times 10^9/L$  to  $> 20 \times 10^9/L$  and by at least 100%. Criteria will be considered modified until week 8 as improvements will not be able to be classed as having lasted at least 8 weeks.

End point type	Secondary
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End point timeframe:

Cycle 1, Week 1

End point values	Cohort 1 (25mg eltrombopag)	Cohort 2 (50mg eltrombopag)	Cohort 3 (100mg eltrombopag)	Cohort 4 (200mg eltrombopag)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	3	4	3
Units: Patients				
No	1	3	4	2
Yes	0	0	0	1

End point values	Cohort 5 (300mg eltrombopag)			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: Patients				
No	12			
Yes	2			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Achievement of Platelet Response according to IWG Criteria - Cycle 1, week 2

End point title	Achievement of Platelet Response according to IWG Criteria - Cycle 1, week 2
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End point description:

The IWG 2006 criteria. These define platelet response as an absolute increase of  $\geq 30 \times 10^9/L$  for patients starting with  $> 20 \times 10^9/L$  platelets or increase from baseline  $< 20 \times 10^9/L$  to  $> 20 \times 10^9/L$  and by at least 100%. Criteria will be considered modified until week 8 as improvements will not be able to be classed as having lasted at least 8 weeks.

End point type	Secondary
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End point timeframe:

Cycle 1, week 2

End point values	Cohort 1 (25mg eltrombopag)	Cohort 2 (50mg eltrombopag)	Cohort 3 (100mg eltrombopag)	Cohort 4 (200mg eltrombopag)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	3	4	3
Units: Patients				
No	4	2	4	2
Yes	0	1	0	1

<b>End point values</b>	Cohort 5 (300mg eltrombopag)			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: Patients				
No	13			
Yes	1			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Achievement of Platelet Response according to IWG Criteria - Cycle 1, week 3

End point title	Achievement of Platelet Response according to IWG Criteria - Cycle 1, week 3
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End point description:

The IWG 2006 criteria. These define platelet response as an absolute increase of  $\geq 30 \times 10^9/L$  for patients starting with  $> 20 \times 10^9/L$  platelets or increase from baseline  $< 20 \times 10^9/L$  to  $> 20 \times 10^9/L$  and by at least 100%. Criteria will be considered modified until week 8 as improvements will not be able to be classed as having lasted at least 8 weeks.

End point type	Secondary
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End point timeframe:

Cycle 1, week 3

<b>End point values</b>	Cohort 1 (25mg eltrombopag)	Cohort 2 (50mg eltrombopag)	Cohort 3 (100mg eltrombopag)	Cohort 4 (200mg eltrombopag)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	3	4	3
Units: Patients				
No	4	1	4	1
Yes	0	2	0	2

<b>End point values</b>	Cohort 5 (300mg eltrombopag)			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: Patients				
No	13			
Yes	1			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Achievement of Platelet Response according to IWG Criteria - Cycle 1, week 4

End point title	Achievement of Platelet Response according to IWG Criteria - Cycle 1, week 4
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End point description:

The IWG 2006 criteria. These define platelet response as an absolute increase of  $\geq 30 \times 10^9/L$  for patients starting with  $> 20 \times 10^9/L$  platelets or increase from baseline  $< 20 \times 10^9/L$  to  $> 20 \times 10^9/L$  and by at least 100%. Criteria will be considered modified until week 8 as improvements will not be able to be classed as having lasted at least 8 weeks.

End point type	Secondary
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End point timeframe:

Cycle 1, week 4

End point values	Cohort 1 (25mg eltrombopag)	Cohort 2 (50mg eltrombopag)	Cohort 3 (100mg eltrombopag)	Cohort 4 (200mg eltrombopag)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	3	4	3
Units: Patients				
No	3	2	4	2
Yes	1	1	0	1

End point values	Cohort 5 (300mg eltrombopag)			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: Patients				
No	12			
Yes	2			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Achievement of Platelet Response according to IWG Criteria - Cycle 1, week 5

End point title	Achievement of Platelet Response according to IWG Criteria - Cycle 1, week 5
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End point description:

The IWG 2006 criteria. These define platelet response as an absolute increase of  $\geq 30 \times 10^9/L$  for patients starting with  $> 20 \times 10^9/L$  platelets or increase from baseline  $< 20 \times 10^9/L$  to  $> 20 \times 10^9/L$  and by at least 100%. Criteria will be considered modified until week 8 as improvements will not be able to be classed as having lasted at least 8 weeks.

End point type	Secondary
End point timeframe:	
Cycle 1, Week 5	

End point values	Cohort 1 (25mg eltrombopag)	Cohort 2 (50mg eltrombopag)	Cohort 3 (100mg eltrombopag)	Cohort 4 (200mg eltrombopag)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	4	3
Units: Patients				
No	2	2	2	1
Yes	1	1	2	2

End point values	Cohort 5 (300mg eltrombopag)			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: Patients				
No	8			
Yes	6			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Achievement of Platelet Response according to IWG Criteria - Cycle 2, week 1

End point title	Achievement of Platelet Response according to IWG Criteria - Cycle 2, week 1
End point description:	
The IWG 2006 criteria. These define platelet response as an absolute increase of $\geq 30 \times 10^9/L$ for patients starting with $> 20 \times 10^9/L$ platelets or increase from baseline $< 20 \times 10^9/L$ to $> 20 \times 10^9/L$ and by at least 100%. Criteria will be considered modified until week 8 as improvements will not be able to be classed as having lasted at least 8 weeks.	
End point type	Secondary
End point timeframe:	
Cycle 2, Week 1	



End point values	Cohort 1 (25mg eltrombopag)	Cohort 2 (50mg eltrombopag)	Cohort 3 (100mg eltrombopag)	Cohort 4 (200mg eltrombopag)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	3	4	3
Units: Patients				
No	2	1	2	2
Yes	0	2	2	1

End point values	Cohort 5 (300mg eltrombopag)			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: Patients				
No	6			
Yes	6			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Achievement of Platelet Response according to IWG Criteria - Cycle 2, week 2

End point title	Achievement of Platelet Response according to IWG Criteria - Cycle 2, week 2
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End point description:

The IWG 2006 criteria. These define platelet response as an absolute increase of  $\geq 30 \times 10^9/L$  for patients starting with  $> 20 \times 10^9/L$  platelets or increase from baseline  $< 20 \times 10^9/L$  to  $> 20 \times 10^9/L$  and by at least 100%. Criteria will be considered modified until week 8 as improvements will not be able to be classed as having lasted at least 8 weeks.

End point type	Secondary
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End point timeframe:

Cycle 2, week 2

End point values	Cohort 1 (25mg eltrombopag)	Cohort 2 (50mg eltrombopag)	Cohort 3 (100mg eltrombopag)	Cohort 4 (200mg eltrombopag)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	3	4	2
Units: Patients				
No	2	0	2	1
Yes	0	3	2	1

<b>End point values</b>	Cohort 5 (300mg eltrombopag)			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: Patients				
No	8			
Yes	4			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Achievement of Platelet Response according to IWG Criteria - Cycle 2, week 3

End point title	Achievement of Platelet Response according to IWG Criteria - Cycle 2, week 3
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End point description:

The IWG 2006 criteria. These define platelet response as an absolute increase of  $\geq 30 \times 10^9/L$  for patients starting with  $> 20 \times 10^9/L$  platelets or increase from baseline  $< 20 \times 10^9/L$  to  $> 20 \times 10^9/L$  and by at least 100%. Criteria will be considered modified until week 8 as improvements will not be able to be classed as having lasted at least 8 weeks.

End point type	Secondary
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End point timeframe:

Cycle 2, week 3

<b>End point values</b>	Cohort 1 (25mg eltrombopag)	Cohort 2 (50mg eltrombopag)	Cohort 3 (100mg eltrombopag)	Cohort 4 (200mg eltrombopag)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	3	4	2
Units: Patients				
No	1	1	2	1
Yes	0	2	2	1

<b>End point values</b>	Cohort 5 (300mg eltrombopag)			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: Patients				
No	7			
Yes	4			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Achievement of Platelet Response according to IWG Criteria - Cycle 2, week 4

End point title	Achievement of Platelet Response according to IWG Criteria - Cycle 2, week 4
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End point description:

The IWG 2006 criteria. These define platelet response as an absolute increase of  $\geq 30 \times 10^9/L$  for patients starting with  $> 20 \times 10^9/L$  platelets or increase from baseline  $< 20 \times 10^9/L$  to  $> 20 \times 10^9/L$  and by at least 100%. Criteria will be considered modified until week 8 as improvements will not be able to be classed as having lasted at least 8 weeks.

End point type	Secondary
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End point timeframe:

Cycle 2, week 4

End point values	Cohort 1 (25mg eltrombopag)	Cohort 2 (50mg eltrombopag)	Cohort 3 (100mg eltrombopag)	Cohort 4 (200mg eltrombopag)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	3	4	2
Units: Patients				
No	1	0	1	1
Yes	0	3	3	1

End point values	Cohort 5 (300mg eltrombopag)			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: Patients				
No	7			
Yes	4			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Achievement of Platelet Response according to IWG Criteria - Cycle 3, week 1

End point title	Achievement of Platelet Response according to IWG Criteria - Cycle 3, week 1
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End point description:

The IWG 2006 criteria. These define platelet response as an absolute increase of  $\geq 30 \times 10^9/L$  for patients starting with  $> 20 \times 10^9/L$  platelets or increase from baseline  $< 20 \times 10^9/L$  to  $> 20 \times 10^9/L$  and by at least 100%. Criteria will be considered modified until week 8 as improvements will not be able to be classed as having lasted at least 8 weeks.

End point type	Secondary
End point timeframe:	
Cycle 3, week 1	

End point values	Cohort 1 (25mg eltrombopag)	Cohort 2 (50mg eltrombopag)	Cohort 3 (100mg eltrombopag)	Cohort 4 (200mg eltrombopag)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	3	4	2
Units: Patients				
No	1	0	1	1
Yes	0	3	3	1

End point values	Cohort 5 (300mg eltrombopag)			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: Patients				
No	5			
Yes	6			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Achievement of Platelet Response according to IWG Criteria - Cycle 3, week 2

End point title	Achievement of Platelet Response according to IWG Criteria - Cycle 3, week 2
End point description:	
The IWG 2006 criteria. These define platelet response as an absolute increase of $\geq 30 \times 10^9/L$ for patients starting with $> 20 \times 10^9/L$ platelets or increase from baseline $< 20 \times 10^9/L$ to $> 20 \times 10^9/L$ and by at least 100%. Criteria will be considered modified until week 8 as improvements will not be able to be classed as having lasted at least 8 weeks.	
End point type	Secondary
End point timeframe:	
Cycle 3, week 2	

End point values	Cohort 1 (25mg eltrombopag)	Cohort 2 (50mg eltrombopag)	Cohort 3 (100mg eltrombopag)	Cohort 4 (200mg eltrombopag)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	3	4	2
Units: Patients				
No	1	0	1	1
Yes	0	3	3	1

End point values	Cohort 5 (300mg eltrombopag)			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: Patients				
No	6			
Yes	5			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Achievement of Platelet Response according to IWG Criteria - Cycle 3, week 3

End point title	Achievement of Platelet Response according to IWG Criteria - Cycle 3, week 3
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End point description:

The IWG 2006 criteria. These define platelet response as an absolute increase of  $\geq 30 \times 10^9/L$  for patients starting with  $> 20 \times 10^9/L$  platelets or increase from baseline  $< 20 \times 10^9/L$  to  $> 20 \times 10^9/L$  and by at least 100%. Criteria will be considered modified until week 8 as improvements will not be able to be classed as having lasted at least 8 weeks.

End point type	Secondary
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End point timeframe:

Cycle 3, week 3

End point values	Cohort 1 (25mg eltrombopag)	Cohort 2 (50mg eltrombopag)	Cohort 3 (100mg eltrombopag)	Cohort 4 (200mg eltrombopag)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	3	4	2
Units: Patients				
No	1	1	1	1
Yes	0	2	3	1

<b>End point values</b>	Cohort 5 (300mg eltrombopag)			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: Patients				
No	7			
Yes	4			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Achievement of Platelet Response according to IWG Criteria - Cycle 3, week 4

End point title	Achievement of Platelet Response according to IWG Criteria - Cycle 3, week 4
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End point description:

The IWG 2006 criteria. These define platelet response as an absolute increase of  $\geq 30 \times 10^9/L$  for patients starting with  $> 20 \times 10^9/L$  platelets or increase from baseline  $< 20 \times 10^9/L$  to  $> 20 \times 10^9/L$  and by at least 100%. Criteria will be considered modified until week 8 as improvements will not be able to be classed as having lasted at least 8 weeks.

End point type	Secondary
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End point timeframe:

Cycle 3, week 4

<b>End point values</b>	Cohort 1 (25mg eltrombopag)	Cohort 2 (50mg eltrombopag)	Cohort 3 (100mg eltrombopag)	Cohort 4 (200mg eltrombopag)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	3	4	2
Units: Patients				
No	1	1	2	1
Yes	0	2	2	1

<b>End point values</b>	Cohort 5 (300mg eltrombopag)			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: Patients				
No	6			
Yes	5			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Achievement of Platelet Response according to IWG Criteria - Cycle 4

End point title	Achievement of Platelet Response according to IWG Criteria - Cycle 4
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End point description:

The IWG 2006 criteria. These define platelet response as an absolute increase of  $\geq 30 \times 10^9/L$  for patients starting with  $> 20 \times 10^9/L$  platelets or increase from baseline  $< 20 \times 10^9/L$  to  $> 20 \times 10^9/L$  and by at least 100%. Criteria will be considered modified until week 8 as improvements will not be able to be classed as having lasted at least 8 weeks.

End point type	Secondary
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End point timeframe:

Cycle 4

End point values	Cohort 1 (25mg eltrombopag)	Cohort 2 (50mg eltrombopag)	Cohort 3 (100mg eltrombopag)	Cohort 4 (200mg eltrombopag)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	3	3	2
Units: Patients				
No	1	0	1	1
Yes	0	3	2	1

End point values	Cohort 5 (300mg eltrombopag)			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: Patients				
No	3			
Yes	8			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Achievement of Platelet Response according to IWG Criteria - Cycle 5

End point title	Achievement of Platelet Response according to IWG Criteria - Cycle 5
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End point description:

The IWG 2006 criteria. These define platelet response as an absolute increase of  $\geq 30 \times 10^9/L$  for patients starting with  $> 20 \times 10^9/L$  platelets or increase from baseline  $< 20 \times 10^9/L$  to  $> 20 \times 10^9/L$  and by at least 100%. Criteria will be considered modified until week 8 as improvements will not be able to be classed as having lasted at least 8 weeks.

End point type	Secondary
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End point timeframe:

Cycle 5

End point values	Cohort 1 (25mg eltrombopag)	Cohort 2 (50mg eltrombopag)	Cohort 3 (100mg eltrombopag)	Cohort 4 (200mg eltrombopag)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	3	3	2
Units: Patients				
No	1	1	1	1
Yes	0	2	2	1

End point values	Cohort 5 (300mg eltrombopag)			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: Patients				
No	3			
Yes	8			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Achievement of Platelet Response according to IWG Criteria - Cycle 6

End point title	Achievement of Platelet Response according to IWG Criteria - Cycle 6
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End point description:

The IWG 2006 criteria. These define platelet response as an absolute increase of  $\geq 30 \times 10^9/L$  for patients starting with  $> 20 \times 10^9/L$  platelets or increase from baseline  $< 20 \times 10^9/L$  to  $> 20 \times 10^9/L$  and by at least 100%. Criteria will be considered modified until week 8 as improvements will not be able to be classed as having lasted at least 8 weeks.

End point type	Secondary
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End point timeframe:

Cycle 6

End point values	Cohort 1 (25mg eltrombopag)	Cohort 2 (50mg eltrombopag)	Cohort 3 (100mg eltrombopag)	Cohort 4 (200mg eltrombopag)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	3	3	2
Units: Patients				
No	1	0	2	1



Yes	0	3	1	1
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End point values	Cohort 5 (300mg eltrombopag)			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: Patients				
No	4			
Yes	5			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Activity of MDS treatment per IWG response criteria

End point title	Activity of MDS treatment per IWG response criteria
End point description:	
Disease response at cycle 3 according to IWG response criteria	
End point type	Secondary
End point timeframe:	
Cycle 3	

End point values	Cohort 1 (25mg eltrombopag)	Cohort 2 (50mg eltrombopag)	Cohort 3 (100mg eltrombopag)	Cohort 4 (200mg eltrombopag)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	3	4	4
Units: Patients				
Complete Remission	0	0	1	0
Marrow CR	0	0	2	0
Partial Remission	0	1	0	0
Stable Disease	0	2	1	2
Disease Progression	1	0	0	0
Missing, no response assumed	4	0	0	2

End point values	Cohort 5 (300mg eltrombopag)			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: Patients				
Complete Remission	2			

Marrow CR	2			
Partial Remission	2			
Stable Disease	4			
Disease Progression	1			
Missing, no response assumed	4			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Activity of MDS treatment per IWG response criteria

End point title Activity of MDS treatment per IWG response criteria

End point description:

Disease Assessment according to IWG response criteria at Cycle 6

End point type Secondary

End point timeframe:

Cycle 6

End point values	Cohort 1 (25mg eltrombopag)	Cohort 2 (50mg eltrombopag)	Cohort 3 (100mg eltrombopag)	Cohort 4 (200mg eltrombopag)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	3	4	4
Units: Patients				
Complete Remission	0	1	0	0
Marrow CR	0	1	0	0
Partial remission	0	0	1	0
Stable disease	0	0	1	2
Disease progression	1	0	1	0
Missing, no response assumed	4	1	1	2

End point values	Cohort 5 (300mg eltrombopag)			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: Patients				
Complete Remission	2			
Marrow CR	3			
Partial remission	1			
Stable disease	2			
Disease progression	0			
Missing, no response assumed	7			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Bone marrow blast percentage - Morphology - Cycle 3

End point title Bone marrow blast percentage - Morphology - Cycle 3

End point description:

End point type Secondary

End point timeframe:

Cycle 3

End point values	Cohort 1 (25mg eltrombopag)	Cohort 2 (50mg eltrombopag)	Cohort 3 (100mg eltrombopag)	Cohort 4 (200mg eltrombopag)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	2	3	2
Units: percent				
median (full range (min-max))	11 (11 to 11)	3.5 (3 to 4)	10 (1 to 11)	15 (14 to 16)

End point values	Cohort 5 (300mg eltrombopag)			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: percent				
median (full range (min-max))	5 (0 to 49)			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Bone marrow blast percentage - Trepine - Cycle 3

End point title Bone marrow blast percentage - Trepine - Cycle 3

End point description:

End point type Secondary

End point timeframe:

Cycle 3

End point values	Cohort 1 (25mg eltrombopag)	Cohort 2 (50mg eltrombopag)	Cohort 3 (100mg eltrombopag)	Cohort 4 (200mg eltrombopag)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0 <sup>[4]</sup>	2	2	0 <sup>[5]</sup>
Units: percent				
median (full range (min-max))	( to )	5 (5 to 5)	9 (8 to 10)	( to )

Notes:

[4] - Trephine not measured at cycle 3 for any patients in cohort 1

[5] - No trephine assessments for this cohort at cycle 3

End point values	Cohort 5 (300mg eltrombopag)			
Subject group type	Reporting group			
Number of subjects analysed	4			
Units: percent				
median (full range (min-max))	5 (0 to 30)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Bone marrow blast percentage - Immunophenotyping - Cycle 3

End point title	Bone marrow blast percentage - Immunophenotyping - Cycle 3
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End point description:

End point type	Secondary
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End point timeframe:

Cycle 3

End point values	Cohort 1 (25mg eltrombopag)	Cohort 2 (50mg eltrombopag)	Cohort 3 (100mg eltrombopag)	Cohort 4 (200mg eltrombopag)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	3	3	1
Units: percent				
median (full range (min-max))	12 (12 to 12)	9 (4 to 15)	11 (1 to 14)	11 (11 to 11)

End point values	Cohort 5 (300mg eltrombopag)			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: percent				
median (full range (min-max))	0.5 (0 to 25)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Bone marrow blast percentage - Morphology - Cycle 6

End point title	Bone marrow blast percentage - Morphology - Cycle 6
End point description:	
End point type	Secondary
End point timeframe:	
Cycle 6	

End point values	Cohort 1 (25mg eltrombopag)	Cohort 2 (50mg eltrombopag)	Cohort 3 (100mg eltrombopag)	Cohort 4 (200mg eltrombopag)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0 <sup>[6]</sup>	2	2	2
Units: percent				
median (full range (min-max))	( to )	0 (0 to 0)	38.5 (0 to 77)	10 (1 to 19)

Notes:

[6] - No morphology assessments measured in this cohort at cycle 6

End point values	Cohort 5 (300mg eltrombopag)			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: percent				
median (full range (min-max))	3 (0 to 5)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Bone marrow blast percentage - Trepine - Cycle 6

End point title	Bone marrow blast percentage - Trepine - Cycle 6
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End point description:

End point type	Secondary
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End point timeframe:

Cycle 6

End point values	Cohort 1 (25mg eltrombopag)	Cohort 2 (50mg eltrombopag)	Cohort 3 (100mg eltrombopag)	Cohort 4 (200mg eltrombopag)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0 <sup>[7]</sup>	2	3	1
Units: percent				
median (full range (min-max))	( to )	2.5 (0 to 5)	10 (5 to 70)	10 (10 to 10)

Notes:

[7] - No trephines assessed for this cohort at cycle 6

End point values	Cohort 5 (300mg eltrombopag)			
Subject group type	Reporting group			
Number of subjects analysed	4			
Units: percent				
median (full range (min-max))	2.5 (0 to 5)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Bone marrow blast percentage - Immunophenotyping - Cycle 6

End point title	Bone marrow blast percentage - Immunophenotyping - Cycle 6
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End point description:

End point type	Secondary
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End point timeframe:

Cycle 6

End point values	Cohort 1 (25mg eltrombopag)	Cohort 2 (50mg eltrombopag)	Cohort 3 (100mg eltrombopag)	Cohort 4 (200mg eltrombopag)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	2	2	1
Units: percent				
median (full range (min-max))	13 (13 to 13)	2.5 (2 to 3)	33.5 (4 to 63)	9 (9 to 9)

<b>End point values</b>	Cohort 5 (300mg eltrombopag)			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: percent				
median (full range (min-max))	1 (0 to 3)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of azacitidine cycles delayed per patient

End point title	Number of azacitidine cycles delayed per patient
End point description:	
End point type	Secondary
End point timeframe:	
During the treatment period	

<b>End point values</b>	Cohort 1 (25mg eltrombopag)	Cohort 2 (50mg eltrombopag)	Cohort 3 (100mg eltrombopag)	Cohort 4 (200mg eltrombopag)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	3	4	3
Units: Number				
number (not applicable)				
0 cycles delayed	4	1	3	3
1 cycle delayed	0	2	0	0
2 cycles delayed	0	0	1	0

<b>End point values</b>	Cohort 5 (300mg eltrombopag)			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: Number				
number (not applicable)				
0 cycles delayed	8			
1 cycle delayed	3			
2 cycles delayed	3			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Length of azacitidine delays

End point title	Length of azacitidine delays
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End point description:

End point type	Secondary
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End point timeframe:

During Treatment

End point values	Cohort 1 (25mg eltrombopag)	Cohort 2 (50mg eltrombopag)	Cohort 3 (100mg eltrombopag)	Cohort 4 (200mg eltrombopag)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	3	4	3
Units: Cycles delayed				
number (not applicable)				
No cycle delay	12	15	21	15
1 day delay	0	0	0	0
7 days delay	0	2	0	0
9 days delay	0	0	0	0
13 days delayed	0	0	0	0
21 days delayed	0	0	0	0
22 days delayed	0	0	0	0

End point values	Cohort 5 (300mg eltrombopag)			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: Cycles delayed				
number (not applicable)				
No cycle delay	56			
1 day delay	3			
7 days delay	1			
9 days delay	1			
13 days delayed	1			
21 days delayed	1			
22 days delayed	1			



## **Statistical analyses**

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse Events were reported from the date of commencement of protocol defined treatment until 30 days after the administration of the last trial treatment.

Assessment type	Non-systematic
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### Dictionary used

Dictionary name	CTCAE
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Dictionary version	4
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### Reporting groups

Reporting group title	All patients
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Reporting group description:

Whilst the defined 'safety population' is defined as patients who received at least one dose of both treatments, the data presented here includes all patients registered to the trial for completeness.

Serious adverse events	All patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	25 / 30 (83.33%)		
number of deaths (all causes)	15		
number of deaths resulting from adverse events	9		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasms benign, malignant and unspecified (incl cysts and polyps) - other			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haematoma			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Thromboembolic event			

subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	5 / 30 (16.67%)		
occurrences causally related to treatment / all	5 / 7		
deaths causally related to treatment / all	0 / 0		
Non-cardiac chest pain			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Immune system disorders - other			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Neutrophil count decreased			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood bilirubin increased			

subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Cardiac disorders			
Left ventricular systolic dysfunction			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Heart failure			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Myocardial infarction			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Movements involuntary			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Intracranial haemorrhage			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	7 / 30 (23.33%)		
occurrences causally related to treatment / all	8 / 8		
deaths causally related to treatment / all	3 / 3		

Anaemia			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Middle ear inflammation			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Gastric haemorrhage			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders - other			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal and urinary disorders - other			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hematuria			

subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Sepsis			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Upper respiratory tract infection			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Skin infection			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Lung infection			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Infections and infestations - other			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tooth infection			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		

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

<b>Non-serious adverse events</b>	All patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	30 / 30 (100.00%)		
Vascular disorders			
Hypotension			
subjects affected / exposed	3 / 30 (10.00%)		
occurrences (all)	4		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	14 / 30 (46.67%)		
occurrences (all)	16		
Injection site reaction			
subjects affected / exposed	11 / 30 (36.67%)		
occurrences (all)	12		
Pyrexia			
subjects affected / exposed	9 / 30 (30.00%)		
occurrences (all)	10		
Edema limbs			
subjects affected / exposed	5 / 30 (16.67%)		
occurrences (all)	5		
General disorders and administration site conditions - other			
subjects affected / exposed	4 / 30 (13.33%)		
occurrences (all)	5		
Flu like symptoms			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	3		
Non-cardiac chest pain			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Pain			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Immune system disorders			
Allergic reaction			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		

Respiratory, thoracic and mediastinal disorders			
Dyspnea			
subjects affected / exposed	7 / 30 (23.33%)		
occurrences (all)	11		
Epistaxis			
subjects affected / exposed	9 / 30 (30.00%)		
occurrences (all)	12		
Respiratory, thoracic and mediastinal disorders - other			
subjects affected / exposed	4 / 30 (13.33%)		
occurrences (all)	4		
Cough			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Pleural effusion			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Psychiatric disorders			
Confusion			
subjects affected / exposed	4 / 30 (13.33%)		
occurrences (all)	4		
Insomnia			
subjects affected / exposed	3 / 30 (10.00%)		
occurrences (all)	3		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	4		
Blood bilirubin increased			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	6		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	5 / 30 (16.67%)		
occurrences (all)	5		
Bruising			



subjects affected / exposed occurrences (all)	3 / 30 (10.00%) 3		
Cardiac disorders			
Chest pain - cardiac subjects affected / exposed occurrences (all)	3 / 30 (10.00%) 3		
Cardiac disorders - Other subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 3		
Nervous system disorders			
Dizziness subjects affected / exposed occurrences (all)	6 / 30 (20.00%) 6		
Headache subjects affected / exposed occurrences (all)	4 / 30 (13.33%) 6		
Lethargy subjects affected / exposed occurrences (all)	4 / 30 (13.33%) 7		
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	8 / 30 (26.67%) 23		
Febrile neutropenia subjects affected / exposed occurrences (all)	7 / 30 (23.33%) 8		
Platelet count decreased subjects affected / exposed occurrences (all)	5 / 30 (16.67%) 13		
Neutrophil count decreased subjects affected / exposed occurrences (all)	7 / 30 (23.33%) 38		
Blood and lymphatic system disorders - Other subjects affected / exposed occurrences (all)	6 / 30 (20.00%) 7		
Ear and labyrinth disorders			

Vertigo subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 2		
Gastrointestinal disorders			
Diarrhea subjects affected / exposed occurrences (all)	15 / 30 (50.00%) 26		
Constipation subjects affected / exposed occurrences (all)	16 / 30 (53.33%) 19		
Nausea subjects affected / exposed occurrences (all)	15 / 30 (50.00%) 18		
Vomiting subjects affected / exposed occurrences (all)	9 / 30 (30.00%) 10		
Abdominal pain subjects affected / exposed occurrences (all)	6 / 30 (20.00%) 7		
Gastrointestinal disorders - other subjects affected / exposed occurrences (all)	5 / 30 (16.67%) 5		
Oral hemorrhage subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 2		
Skin and subcutaneous tissue disorders			
Skin and subcutaneous tissue disorders - other subjects affected / exposed occurrences (all)	6 / 30 (20.00%) 8		
Pruritus subjects affected / exposed occurrences (all)	5 / 30 (16.67%) 6		
Rash maculo-papular subjects affected / exposed occurrences (all)	5 / 30 (16.67%) 7		
Dry skin			

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Purpura</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Skin hyperpigmentation</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>2 / 30 (6.67%)</p> <p>2</p> <p>2 / 30 (6.67%)</p> <p>2</p> <p>2 / 30 (6.67%)</p> <p>3</p>		
<p>Renal and urinary disorders</p> <p>Acute kidney injury</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Hematuria</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>2 / 30 (6.67%)</p> <p>2</p> <p>2 / 30 (6.67%)</p> <p>2</p>		
<p>Musculoskeletal and connective tissue disorders</p> <p>Back pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Musculoskeletal and connective tissue disorders - other</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Arthralgia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>3 / 30 (10.00%)</p> <p>4</p> <p>3 / 30 (10.00%)</p> <p>4</p> <p>2 / 30 (6.67%)</p> <p>2</p>		
<p>Infections and infestations</p> <p>Lung infection</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Sepsis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Skin infection</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Upper respiratory infection</p>	<p>8 / 30 (26.67%)</p> <p>9</p> <p>4 / 30 (13.33%)</p> <p>4</p> <p>3 / 30 (10.00%)</p> <p>3</p>		

subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Infections and infestations - other			
subjects affected / exposed	5 / 30 (16.67%)		
occurrences (all)	7		
Lip infection			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Wound infection			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Metabolism and nutrition disorders			
Hypokalemia			
subjects affected / exposed	3 / 30 (10.00%)		
occurrences (all)	4		
Hypophosphatemia			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	5		
Anorexia nervosa			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 June 2015	Update to eligibility criteria Update to definition of Dose Limiting Toxicity to specify the event must be at least possibly related to eltrombopag. Update to schedule of events - clarifications Update to trial personnel Update to registration phone number Clarification of allowed dose modifications Update to Adverse Event reporting - abnormal laboratory findings do not need to be reported unless they meet specific criteria. Update to CRF list Update to response assessment reporting to include Hematological Improvement according to IWG criteria Update to archiving period Addition of Appendices 7 (Prohibited concomitant medication and 8 (IWG Response Criteria) Minor corrections and clarifications
25 April 2016	Update to trial personnel Update to registration phone number Update to Trial Treatment details (Eltrombopag only) - change from clinical trial stock to commercial supply. Update to definition of Dose Limiting Toxicity to exclude disease progression Update to Adverse Event reporting to include reporting of overdoses Clarification of Sample Collection Update to Data Collection to add Transfusion Form Minor corrections and clarifications

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported