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Clinical Trial Results Website

Sponsor

Novartis Pharmaceuticals

LBH589 (panobinostat) and INC424 (ruxolitinib)

Trial Indication(s)

Primary myelofibrosis (PMF), post-polycythemia vera-myelofibrosis (PPV-MF) or post-essential thrombocythemia-myelofibrosis (PET-MF).

Protocol Number

CLBH589X2106

Protocol Title

A Phase 1b, open-label, multi-center, single arm, dose finding study to assess safety and pharmacokinetics of the oral combination of panobinostat and ruxolitinib in patients with primary myelofibrosis (PMF), post-polycythemia vera-myelofibrosis (PP-MF) or post-essential thrombocythemia-myelofibrosis (PET-MF)

Clinical Trial Phase

Phase 1

Phase of Drug Development

Phase IV

Study Start/End Dates

Study Start Date: 30 November 2011 (Actual)
Primary Completion Date: 22 June 2020 (Actual)
Study Completion Date: 22 June 2020 (Actual)

Study Design/Methodology

This was a Phase 1b, open-label, multi-center, single-arm, dose-finding study to assess the safety of the combination of ruxolitinib and panobinostat, and characterize the PK of this combination in subjects with primary myelofibrosis (PMF), post-polycythemia vera-myelofibrosis (PPV-MF) or post-essential thrombocythemia-myelofibrosis (PET-MF). Panobinostat was administered orally three times a week, every other week, in a 28-day treatment cycle. Starting dose of panobinostat was 10 mg and was intended to go up to 30 mg or higher. Ruxolitinib was administered orally twice a day every day in a 28-day treatment cycle. Starting dose was 5 mg and was intended to go up to 15 mg.

Centers

10 centers in 5 countries: Italy(3), Ireland(1), United Kingdom(1), France(3), Germany(2)

Objectives:

Primary Objective:

To establish the Maximum Tolerated Dose (MTD) and/or Recommended Phase II Dose (RPIID) of the combination of ruxolitinib and panobinostat in subjects with MF

Secondary Objectives:

- To evaluate the safety of the oral co-administration of ruxolitinib and panobinostat in subjects with MF
- To characterize the pharmacokinetics of ruxolitinib at varying doses, as a single agent and when given in combination with panobinostat, to subjects with MF
- To characterize the pharmacokinetics of panobinostat at varying doses, in combination with ruxolitinib, in subjects with MF.

Test Product (s), Dose(s), and Mode(s) of Administration

Panobinostat was administered orally three times a week (TIW) every other week (QOW) in a 28-day treatment cycle. Starting dose of panobinostat was 10 mg and was intended to go up to 30 mg or higher. Ruxolitinib was administered orally twice a day (b.i.d.) every day in a 28-day treatment cycle (Q4wk). Starting dose was 5 mg and was intended to go up to 15 mg.

Statistical Methods

An adaptive Bayesian logistic regression model and dose escalation with overdose control (EWOC) principle similar to that proposed by Babb et al (1998) and Neuenschwander et al (2008) was used to guide the dose escalation to determine the MTD of ruxolitinib in combination with panobinostat. Dose recommendation was based on posterior summaries and the probability that the true DLT rate for each dose combination lay in one of the following categories: [0%, 16%] under-dosing, [16%, 35%] targeted toxicity, and [35%, 100%] excessive toxicity. Following the principle of EWOC, after each cohort of patients, the recommended dose combination was the one with the highest posterior probability of DLT in the target interval [16%, 35%] among the doses fulfilling the overdose criterion where there were less than 25% chance of excessive toxicity.

The MTD was assessed during the first treatment cycle. Historical data from the n=28 subjects who had completed one cycle of single-agent treatment with panobinostat within Study CLBH589B2102 as well as data from the n=117 subjects who started on a single-agent treatment with ruxolitinib at one of 4 BID (twice daily) dose levels within Study CLBH589B2102 were used to derive informative priors for the model parameters for escalation phase.

Each treatment cohort consisted of a minimum of three subjects who were evaluable for the dose-determining set over the first cycle of double-agent treatment. Toxicities were assessed using the National Cancer Institute CTCAE V4.03.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:
- Diagnosis of myelofibrosis, either PMF, PPV or PET MF
- Palpable splenomegaly ≥ 5cm
- May have been previously treated with either panobinostat or ruxolitinib (unless discontinued for clinically relevant toxicities)
- Acceptable lab ranges for all organ systems
- Specifically: Platelet count > 100,000 not reached with the aide of transfusions
- Blast count < 10% at screening
- ECOG ≤ 2
- Must be able to discontinue all drugs being used to treat MF at least 7 days prior to starting study drug

Exclusion Criteria:
- Active malignancy
- Clinically significant heart disease
- Splenic irradiation within 12 months of starting study drug

- Need for ongoing systemic anticoagulation with the exception of Aspirin < 150mg/day or Low Molecular Weight Heparin
- History of platelet dysfunction or bleeding disorder in the 6 months prior to screening
- Patient is at risk for spontaneous bleeding
- Willing and/or eligible for stem-cell transplantation
- Impairment of gastro-intestinal function that may impact the absorption of study treatment
- Other protocol-defined inclusion/exclusion criteria may apply

Participant Flow Table

Overall Study

	Cohort 1: LBH 10mg + INC 5mg (Escalation Phase)	Cohort 2: LBH 10mg + INC 10mg (Escalation Phase)	Cohort 3: LBH 10mg + INC 15mg (Escalation Phase)	Cohort 4: LBH 15mg + INC 15mg (Escalation Phase)	Cohort 5: LBH 20mg + INC 15mg (Escalation Phase)	Cohort 6: LBH 25mg + INC 15mg (Escalation Phase)	Cohort 7: LBH 25mg + INC 15mg (Expansion Phase)	Total
Arm/Group Description	Subjects were treated with panobinostat 10 mg three times per week (TIW) every other week (QOW) and ruxolitinib 5 mg twice daily (BID) on a 28 day cycle	Subjects were treated with and panobinostat 10 mg three times per week (TIW) every other week (QOW) and ruxolitinib 10 mg twice daily (BID) on a 28 day cycle	Subjects were treated with and panobinostat 10 mg three times per week (TIW) every other week (QOW) and ruxolitinib 15 mg twice daily (BID) on a 28 day cycle	Subjects were treated with panobinostat 15 mg three times per week (TIW) every other week (QOW) ruxolitinib and 15 mg twice daily (BID) on a 28 day cycle	Subjects were treated with panobinostat 20 mg three times per week (TIW) every other week (QOW) and ruxolitinib 15 mg twice daily (BID) on a 28 day cycle	Subjects were treated with ruxolitinib 15 mg twice daily (BID) and panobinostat 25 mg three times per week (TIW) every other week (QOW) on a 28 day cycle	Subjects were treated with panobinostat 25 mg three times per week (TIW) every other week (QOW) and ruxolitinib 15 mg twice daily (BID) for at least 2 cycles on a 28 day cycle	
Started	5	8	5	5	4	11	23	61
Completed	0	0	0	0	0	0	0	0
Not Completed	5	8	5	5	4	11	23	61
Adverse Event	2	0	1	3	0	4	6	16

Withdrawal by Subject	1	0	0	0	0	0	2	3
Death	0	0	0	2	2	0	1	5
Protocol Violation	0	0	0	0	0	1	0	1
Administrative problems	0	3	0	0	0	4	3	10
Disease progression	0	3	2	0	2	1	7	15
Follow-up phase completed as per Protocol	2	2	2	0	0	1	4	11

Baseline Characteristics

	Cohort 1: LBH 10mg + INC 5mg (Escalation Phase)	Cohort 2: LBH 10mg + INC 10mg (Escalation Phase)	Cohort 3: LBH 10mg + INC 15mg (Escalation Phase)	Cohort 4: LBH 15mg + INC 15mg (Escalation Phase)	Cohort 5: LBH 20mg + INC 15mg (Escalation Phase)	Cohort 6: LBH 25mg + INC 15mg (Escalation Phase)	Cohort 7: LBH 25mg + INC 15mg (Expansion Phase)	Total
Arm/Group Description	Subjects were treated with panobinostat 10 mg three times per week (TIW) every other week (QOW) and ruxolitinib 5 mg twice daily (BID) on a 28 day cycle	Subjects were treated with and panobinostat 10 mg three times per week (TIW) every other week (QOW) and ruxolitinib 10 mg twice daily (BID) on	Subjects were treated with and panobinostat 10 mg three times per week (TIW) every other week (QOW) and ruxolitinib 15 mg twice daily (BID) on	Subjects were treated with panobinostat 15 mg three times per week (TIW) every other week (QOW) ruxolitinib and 15 mg twice daily (BID) on a 28 day cycle	Subjects were treated with panobinostat 20 mg three times per week (TIW) every other week (QOW) and ruxolitinib 15 mg twice daily (BID) on a 28 day cycle	Subjects were treated with ruxolitinib 15 mg twice daily (BID) and panobinostat 25 mg three times per week (TIW) every other week (QOW) on a 28 day cycle	Subjects were treated with panobinostat 25 mg three times per week (TIW) every other week (QOW) and ruxolitinib 15 mg twice daily (BID) for at least 2	

		a 28 day cycle	a 28 day cycle				cycles on a 28 day cycle	
Number of Participants [units: participants]	5	8	5	5	4	11	23	61
Sex: Female, Male (units: Participants) Count of Participants (Not Applicable)								
Female	2	5	1	2	2	7	7	26
Male	3	3	4	3	2	4	16	35
Age Continuous (units: years) Mean ± Standard Deviation								
	59.2±10.33	62.6±6.52	62.0±9.85	68.8±5.02	66.8±14.38	61.4±4.82	66.0±6.99	64.1±7.76
Age, Customized (units: Participants)								
Adults (18-64 years)	4	5	3	1	2	7	9	31
From 65-84 years	1	3	2	4	2	4	14	30
Race/Ethnicity, Customized (units: Participants)								
Caucasian	5	8	5	5	4	11	23	61

Primary Outcome Result(s)

Incidence rates of dose limiting toxicities (DLTs) in the first cycle of study treatment

(Time Frame: Throughout first cycle on Day 1-Day 28 (a cycle = 28 days))

	Cohort 1: LBH 10mg + INC 5mg (Escalation Phase)	Cohort 2: LBH 10mg + INC 10mg (Escalation Phase)	Cohort 3: LBH 10mg + INC 15mg (Escalation Phase)	Cohort 4: LBH 15mg + INC 15mg (Escalation Phase)	Cohort 5: LBH 20mg + INC 15mg (Escalation Phase)	Cohort 6: LBH 25mg + INC 15mg (Escalation Phase)	Cohort 7: LBH 25mg + INC 15mg (Expansion Phase)
Arm/Group Description	Subjects were treated with panobinostat 10 mg three times per week (TIW) every other week (QOW) and ruxolitinib 5 mg twice daily (BID) on a 28 day cycle	Subjects were treated with and panobinostat 10 mg three times per week (TIW) every other week (QOW) and ruxolitinib 10 mg twice daily (BID) on a 28 day cycle	Subjects were treated with and panobinostat 10 mg three times per week (TIW) every other week (QOW) and ruxolitinib 15 mg twice daily (BID) on a 28 day cycle	Subjects were treated with panobinostat 15 mg three times per week (TIW) every other week (QOW) ruxolitinib and 15 mg twice daily (BID) on a 28 day cycle	Subjects were treated with panobinostat 20 mg three times per week (TIW) every other week (QOW) and ruxolitinib 15 mg twice daily (BID) on a 28 day cycle	Subjects were treated with ruxolitinib 15 mg twice daily (BID) and panobinostat 25 mg three times per week (TIW) every other week (QOW) on a 28 day cycle	Subjects were treated with panobinostat 25 mg three times per week (TIW) every other week (QOW) and ruxolitinib 15 mg twice daily (BID) for at least 2 cycles on a 28 day cycle
Number of Participants Analyzed [units: participants]	5	8	5	4	4	11	23
Incidence rates of dose limiting toxicities (DLTs) in the first cycle of study treatment (units: Number of DLTs)							
Any primary system organ class	0	1	0	0	1	1	0
Gastrointestinal disorders	0	0	0	0	0	1	0
Nausea	0	0	0	0	0	1	0
Blood and lymphatic system disorders	0	1	0	0	1	0	0

Thrombocytopenia	0	1	0	0	1	0	0

Secondary Outcome Result(s)

PK parameter Tmax of ruxolitinib

(Time Frame: Cycle 1 Day 1, Cycle 1 Day 2, Cycle 1 Day 6)

	Cohort 1: LBH 10mg + INC 5mg (Escalation Phase)	Cohort 2: LBH 10mg + INC 10mg (Escalation Phase)	Cohort 3: LBH 10mg + INC 15mg (Escalation Phase)	Cohort 4: LBH 15mg + INC 15mg (Escalation Phase)	Cohort 5: LBH 20mg + INC 15mg (Escalation Phase)	Cohort 6: LBH 25mg + INC 15mg (Escalation Phase)	Cohort 7: LBH 25mg + INC 15mg (Expansion Phase)
Arm/Group Description	Subjects were treated with panobinostat 10 mg three times per week (TIW) every other week (QOW) and ruxolitinib 5 mg twice daily (BID) on a 28 day cycle	Subjects were treated with and panobinostat 10 mg three times per week (TIW) every other week (QOW) and ruxolitinib 10 mg twice daily (BID) on a 28 day cycle	Subjects were treated with and panobinostat 10 mg three times per week (TIW) every other week (QOW) and ruxolitinib 15 mg twice daily (BID) on a 28 day cycle	Subjects were treated with panobinostat 15 mg three times per week (TIW) every other week (QOW) ruxolitinib and 15 mg twice daily (BID) on a 28 day cycle	Subjects were treated with panobinostat 20 mg three times per week (TIW) every other week (QOW) and ruxolitinib 15 mg twice daily (BID) on a 28 day cycle	Subjects were treated with ruxolitinib 15 mg twice daily (BID) and panobinostat 25 mg three times per week (TIW) every other week (QOW) on a 28 day cycle	Subjects were treated with panobinostat 25 mg three times per week (TIW) every other week (QOW) and ruxolitinib 15 mg twice daily (BID) for at least 2 cycles on a 28 day cycle
Number of Participants Analyzed [units: participants]	5	8	5	5	4	11	23
PK parameter Tmax of ruxolitinib (units: hr) Median (Full Range)							
Cycle 1 Day 1 (n= 5,8,5,5,4,11,22)	0.500 (0.500 to 1.00)	0.750 (0.500 to 1.58)	1.00 (0.500 to 1.50)	0.550 (0.500 to 2.00)	1.00 (0.483 to 1.53)	1.00 (0.500 to 3.98)	1.00 (0.500 to 2.00)

Cycle 1 Day 2 (n= 5,8,5,5,4,11,21)	1.00 (0.467 to 1.00)	0.500 (0 to 1.00)	1.00 (0.500 to 1.50)	0.533 (0.500 to 1.47)	0.959 (0.500 to 1.50)	0.833 (0 to 2.02)	0.950 (0.417 to 2.00)
Cycle 1 Day 6 (n= 5,8,5,5,4,11,22)	1.00 (0.550 to 1.00)	1.06 (0.500 to 2.00)	1.50 (1.00 to 2.00)	1.03 (1.00 to 1.57)	0.575 (0.550 to 1.50)	0.550 (0.500 to 2.08)	1.00 (0.500 to 2.08)

PK parameter Cmax of panobinostat

(Time Frame: Panobinostat on Cycle 1 Day 2, Cycle 1 Day 6)

	Cohort 1: LBH 10mg + INC 5mg (Escalation Phase)	**Cohort 2: LBH 10mg + INC 10mg (Escalation Phase)**	**Cohort 3: LBH 10mg + INC 15mg (Escalation Phase)**	**Cohort 4: LBH 15mg + INC 15mg (Escalation Phase)**	**Cohort 5: LBH 20mg + INC 15mg (Escalation Phase)**	**Cohort 6: LBH 25mg + INC 15mg (Escalation Phase)**	**Cohort 7: LBH 25mg + INC 15mg (Expansion Phase)**
Arm/Group Description	Subjects were treated with panobinostat 10 mg three times per week (TIW) every other week (QOW) and ruxolitinib 5 mg twice daily (BID) on a 28 day cycle	Subjects were treated with and panobinostat 10 mg three times per week (TIW) every other week (QOW) and ruxolitinib 10 mg twice daily (BID) on a 28 day cycle	Subjects were treated with and panobinostat 10 mg three times per week (TIW) every other week (QOW) and ruxolitinib 15 mg twice daily (BID) on a 28 day cycle	Subjects were treated with panobinostat 15 mg three times per week (TIW) every other week (QOW) ruxolitinib and 15 mg twice daily (BID) on a 28 day cycle	Subjects were treated with panobinostat 20 mg three times per week (TIW) every other week (QOW) and ruxolitinib 15 mg twice daily (BID) on a 28 day cycle	Subjects were treated with ruxolitinib 15 mg twice daily (BID) and panobinostat 25 mg three times per week (TIW) every other week (QOW) on a 28 day cycle	Subjects were treated with panobinostat 25 mg three times per week (TIW) every other week (QOW) and ruxolitinib 15 mg twice daily (BID) for at least 2 cycles on a 28 day cycle
Number of Participants Analyzed [units: participants]	5	8	5	5	4	11	23
PK parameter Cmax of panobinostat (units: ng/mL) Geometric Mean (Geometric Coefficient of Variation)							
Cycle 1 Day 2 (n =5,8,5,5,4,11,21)	2.54 (35.8%)	4.97 (108.9%)	2.34 (70.8%)	7.85 (66.2%)	7.83 (63.3%)	12.4 (129.0%)	9.89 (71.7%)

Cycle 1 Day 6 (n =5,8,5,5,4,11,21)	2.79 (50.1%)	5.26 (62.0%)	3.02 (41.6%)	4.07 (63.4%)	7.93 (103.9%)	17.6 (87.4%)	10.3 (100.5%)

PK parameter Cmax of ruxolitinib

(Time Frame: Cycle 1 Day 1, Cycle 1 Day 2, Cycle 1 Day 6)

	Cohort 1: LBH 10mg + INC 5mg (Escalation Phase)	Cohort 2: LBH 10mg + INC 10mg (Escalation Phase)	Cohort 3: LBH 10mg + INC 15mg (Escalation Phase)	Cohort 4: LBH 15mg + INC 15mg (Escalation Phase)	Cohort 5: LBH 20mg + INC 15mg (Escalation Phase)	Cohort 6: LBH 25mg + INC 15mg (Escalation Phase)	Cohort 7: LBH 25mg + INC 15mg (Expansion Phase)
Arm/Group Description	Subjects were treated with panobinostat 10 mg three times per week (TIW) every other week (QOW) and ruxolitinib 5 mg twice daily (BID) on a 28 day cycle	Subjects were treated with and panobinostat 10 mg three times per week (TIW) every other week (QOW) and ruxolitinib 10 mg twice daily (BID) on a 28 day cycle	Subjects were treated with and panobinostat 10 mg three times per week (TIW) every other week (QOW) and ruxolitinib 15 mg twice daily (BID) on a 28 day cycle	Subjects were treated with panobinostat 15 mg three times per week (TIW) every other week (QOW) ruxolitinib and 15 mg twice daily (BID) on a 28 day cycle	Subjects were treated with panobinostat 20 mg three times per week (TIW) every other week (QOW) and ruxolitinib 15 mg twice daily (BID) on a 28 day cycle	Subjects were treated with ruxolitinib 15 mg twice daily (BID) and panobinostat 25 mg three times per week (TIW) every other week (QOW) on a 28 day cycle	Subjects were treated with panobinostat 25 mg three times per week (TIW) every other week (QOW) and ruxolitinib 15 mg twice daily (BID) for at least 2 cycles on a 28 day cycle
Number of Participants Analyzed [units: participants]	5	8	5	5	4	11	23
PK parameter Cmax of ruxolitinib (units: ng/mL) Geometric Mean (Geometric Coefficient of Variation)							
Cycle 1 Day1 (n=5,8,5,5,4,11,22)	34.9 (25.1%)	126 (49.9%)	151 (27.4%)	203 (24.3%)	92.8 (16.2%)	162 (39.3%)	161 (35.9%)
Cycle 1 Day 2 (n=5,8,5,5,4,11,21)	40.7 (24.1%)	71.6 (261.4%)	133 (42.1%)	170 (36.1%)	112 (17.7%)	174 (38.2%)	170 (38.7%)

Cycle 1 Day 6 (n=5,8,5,5,4,11,22)	52.2 (37.2%)	122 (51.9%)	145 (26.7%)	176 (44.3%)	104 (46.5%)	244 (42.6%)	169 (46.4%)

PK parameter Tmax of panobinostat

(Time Frame: Cycle 1 Day 2, Cycle 1 Day 6)

	Cohort 1: LBH 10mg + INC 5mg (Escalation Phase)	Cohort 2: LBH 10mg + INC 10mg (Escalation Phase)	Cohort 3: LBH 10mg + INC 15mg (Escalation Phase)	Cohort 4: LBH 15mg + INC 15mg (Escalation Phase)	Cohort 5: LBH 20mg + INC 15mg (Escalation Phase)	Cohort 6: LBH 25mg + INC 15mg (Escalation Phase)	Cohort 7: LBH 25mg + INC 15mg (Expansion Phase)
Arm/Group Description	Subjects were treated with panobinostat 10 mg three times per week (TIW) every other week (QOW) and ruxolitinib 5 mg twice daily (BID) on a 28 day cycle	Subjects were treated with and panobinostat 10 mg three times per week (TIW) every other week (QOW) and ruxolitinib 10 mg twice daily (BID) on a 28 day cycle	Subjects were treated with and panobinostat 10 mg three times per week (TIW) every other week (QOW) and ruxolitinib 15 mg twice daily (BID) on a 28 day cycle	Subjects were treated with panobinostat 15 mg three times per week (TIW) every other week (QOW) ruxolitinib and 15 mg twice daily (BID) on a 28 day cycle	Subjects were treated with panobinostat 20 mg three times per week (TIW) every other week (QOW) and ruxolitinib 15 mg twice daily (BID) on a 28 day cycle	Subjects were treated with ruxolitinib 15 mg twice daily (BID) and panobinostat 25 mg three times per week (TIW) every other week (QOW) on a 28 day cycle	Subjects were treated with panobinostat 25 mg three times per week (TIW) every other week (QOW) and ruxolitinib 15 mg twice daily (BID) for at least 2 cycles on a 28 day cycle
Number of Participants Analyzed [units: participants]	5	8	5	5	4	11	23
PK parameter Tmax of panobinostat (units: hr) Median (Full Range)							
Cycle 1 Day 2 (n = 5,8,5,5,4,11,21)	1.50 (0.967 to 2.00)	0.750 (0.500 to 2.08)	1.50 (0.500 to 4.00)	1.00 (0.467 to 1.97)	0.959 (0.500 to 1.50)	1.00 (0.483 to 4.00)	1.50 (0.450 to 6.92)
Cycle 1 Day 6 (n = 5,8,5,5,4,11,21)	1.50 (0.500 to 2.00)	1.71 (0.500 to 4.00)	1.50 (0.500 to 2.07)	1.03 (1.00 to 2.00)	1.25 (0.567 to 4.00)	1.00 (0.550 to 2.08)	1.50 (0.500 to 4.08)

PK parameter AUCinf of panobinostat

(Time Frame: Cycle 1 Day 2, Cycle 1 Day 6)

	Cohort 1: LBH 10mg + INC 5mg (Escalation Phase)	Cohort 2: LBH 10mg + INC 10mg (Escalation Phase)	Cohort 3: LBH 10mg + INC 15mg (Escalation Phase)	Cohort 4: LBH 15mg + INC 15mg (Escalation Phase)	Cohort 5: LBH 20mg + INC 15mg (Escalation Phase)	Cohort 6: LBH 25mg + INC 15mg (Escalation Phase)	Cohort 7: LBH 25mg + INC 15mg (Expansion Phase)
Arm/Group Description	Subjects were treated with panobinostat 10 mg three times per week (TIW) every other week (QOW) and ruxolitinib 5 mg twice daily (BID) on a 28 day cycle	Subjects were treated with and panobinostat 10 mg three times per week (TIW) every other week (QOW) and ruxolitinib 10 mg twice daily (BID) on a 28 day cycle	Subjects were treated with and panobinostat 10 mg three times per week (TIW) every other week (QOW) and ruxolitinib 15 mg twice daily (BID) on a 28 day cycle	Subjects were treated with panobinostat 15 mg three times per week (TIW) every other week (QOW) ruxolitinib and 15 mg twice daily (BID) on a 28 day cycle	Subjects were treated with panobinostat 20 mg three times per week (TIW) every other week (QOW) and ruxolitinib 15 mg twice daily (BID) on a 28 day cycle	Subjects were treated with ruxolitinib 15 mg twice daily (BID) and panobinostat 25 mg three times per week (TIW) every other week (QOW) on a 28 day cycle	Subjects were treated with panobinostat 25 mg three times per week (TIW) every other week (QOW) and ruxolitinib 15 mg twice daily (BID) for at least 2 cycles on a 28 day cycle
Number of Participants Analyzed [units: participants]	5	8	5	5	4	11	23
PK parameter AUCinf of panobinostat (units: h*ng/mL) Geometric Mean (Geometric Coefficient of Variation)							
Cycle 1 Day 2 (n = 4,7,3,5,4,11,21)	17.3 (66.8%)	32.5 (61.9%)	19.4 (7.3%)	43.8 (65.7%)	52.0 (33.4%)	55.5 (154.5%)	65.9 (34.9%)
Cycle 1 Day 6 (n = 4,4,4,3,3,7,15)	23.8 (34.1%)	46.4 (34.4%)	21.2 (20.2%)	47.5 (98.6%)	61.3 (52.1%)	81.7 (53.7%)	88.9 (36.3%)

PK parameters AUC0-12 and AUClast of ruxolitinib

(Time Frame: Cycle 1 Day 1, Cycle 1 Day 2, Cycle 1 Day 6)

	Cohort 1: LBH 10mg + INC 5mg (Escalation Phase)	Cohort 2: LBH 10mg + INC 10mg (Escalation Phase)	Cohort 3: LBH 10mg + INC 15mg (Escalation Phase)	Cohort 4: LBH 15mg + INC 15mg (Escalation Phase)	Cohort 5: LBH 20mg + INC 15mg (Escalation Phase)	Cohort 6: LBH 25mg + INC 15mg (Escalation Phase)	Cohort 7: LBH 25mg + INC 15mg (Expansion Phase)
Arm/Group Description	Subjects were treated with panobinostat 10 mg three times per week (TIW) every other week (QOW) and ruxolitinib 5 mg twice daily (BID) on a 28 day cycle	Subjects were treated with and panobinostat 10 mg three times per week (TIW) every other week (QOW) and ruxolitinib 10 mg twice daily (BID) on a 28 day cycle	Subjects were treated with and panobinostat 10 mg three times per week (TIW) every other week (QOW) and ruxolitinib 15 mg twice daily (BID) on a 28 day cycle	Subjects were treated with panobinostat 15 mg three times per week (TIW) every other week (QOW) ruxolitinib and 15 mg twice daily (BID) on a 28 day cycle	Subjects were treated with panobinostat 20 mg three times per week (TIW) every other week (QOW) and ruxolitinib 15 mg twice daily (BID) on a 28 day cycle	Subjects were treated with ruxolitinib 15 mg twice daily (BID) and panobinostat 25 mg three times per week (TIW) every other week (QOW) on a 28 day cycle	Subjects were treated with panobinostat 25 mg three times per week (TIW) every other week (QOW) and ruxolitinib 15 mg twice daily (BID) for at least 2 cycles on a 28 day cycle
Number of Participants Analyzed [units: participants]	5	8	5	5	4	11	23
PK parameters AUC0-12 and AUClast of ruxolitinib (units: h*ng/mL) Geometric Mean (Geometric Coefficient of Variation)							
C1D1: AUC0-12 (n= 5,8,5,5,4,10,22)	121 (15.6%)	326 (38.2%)	408 (22.5%)	574 (48.0%)	274 (25.9%)	506 (41.8%)	532 (36.9%)
C1D2: AUC0-12 (n= 5,8,5,5,4,9,15)	140 (15.8%)	206 (256.2%)	498 (27.2%)	635 (15.8%)	335 (13.9%)	536 (35.7%)	579 (46.2%)
C1D6: AUC0-12 (n= 5,6,3,5,4,10,16)	144 (30.6%)	510 (35.3%)	515 (23.1%)	708 (27.0%)	342 (31.0%)	745 (48.8%)	654 (52.4%)
C1D1: AUClast (n= 5,8,5,5,4,11,22)	109 (15.3%)	313 (37.8%)	392 (23.2%)	538 (45.8%)	261 (22.8%)	468 (39.2%)	487 (34.2%)
C1D2: AUClast (n= 5,8,5,5,4,11,21)	128 (12.9%)	189 (262.8%)	439 (26.5%)	559 (14.6%)	307 (11.1%)	499 (32.9%)	531 (40.6%)

C1D6: AUClast (n= 5,8,5,5,4,11,22)	132 (27.3%)	404 (44.1%)	475 (21.1%)	621 (28.3%)	304 (29.1%)	658 (45.9%)	536 (48.8%)

Safety Results

All-Cause Mortality

	Cohort 1: LBH 10mg + INC 5mg (Escalation Phase) N = 5	Cohort 2: LBH 10mg + INC 10mg (Escalation Phase) N = 8	Cohort 3: LBH 10mg + INC 15mg (Escalation Phase) N = 5	Cohort 4: LBH 15mg + INC 15mg (Escalation Phase) N = 5	Cohort 5: LBH 20mg + INC 15mg (Escalation Phase) N = 4	Cohort 6: LBH 25mg + INC 15mg (Escalation Phase) N = 11	All patients (Escalation phase) N = 38	Cohort 7: LBH 25mg + INC 15mg (Expansion Phase) N = 23	All Patients (MTD/RPIID) N = 34	Total Patients N = 61
Arm/Group Description	Subjects were treated with panobinostat 10 mg three times per week (TIW) every other week (QOW) and ruxolitinib 5 mg twice daily (BID) on a 28 day cycle	Subjects were treated with and panobinost at 10 mg three times per week (TIW) every other week (QOW) and ruxolitinib 10 mg twice daily (BID) on a 28 day cycle	Subjects were treated with and panobinost at 10 mg three times per week (TIW) every other week (QOW) and ruxolitinib 15 mg twice daily (BID) on a 28 day cycle	Subjects were treated with panobinost at 15 mg three times per week (TIW) every other week (QOW) ruxolitinib and 15 mg twice daily (BID) on a 28 day cycle	Subjects were treated with panobinost at 20 mg three times per week (TIW) every other week (QOW) and ruxolitinib 15 mg twice daily (BID) on a 28 day cycle	Subjects were treated with ruxolitinib 15 mg twice daily (BID) and panobinost at 25 mg three times per week (TIW) every other week (QOW) on a 28 day cycle	All patients in the Escalation phase	Subjects were treated with panobinost at 25 mg three times per week (TIW) every other week (QOW) and ruxolitinib 15 mg twice daily (BID) for at least 2 cycles on a 28 day cycle	All Patients in the maximum tolerated dose/ recommended phase 2 dose groups	All patients in the study

Total participants affected	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (40.00%)	0 (0.00%)	0 (0.00%)	2 (5.26%)	1 (4.35%)	1 (2.94%)	3 (4.92%)

Serious Adverse Events by System Organ Class

Time Frame	Adverse Events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV).
Source Vocabulary for Table Default	MedDRA (23.0)
Assessment Type for Table Default	Systematic Assessment

	Cohort 1: LBH 10mg + INC 5mg (Escalation Phase) N = 5	**Cohort 2: LBH 10mg + INC 10mg (Escalation Phase) N = 8**	**Cohort 3: LBH 10mg + INC 15mg (Escalation Phase) N = 5**	**Cohort 4: LBH 15mg + INC 15mg (Escalation Phase) N = 5**	**Cohort 5: LBH 20mg + INC 15mg (Escalation Phase) N = 4**	**Cohort 6: LBH 25mg + INC 15mg (Escalation Phase) N = 11**	**All patients (Escalation phase) N = 38**	**Cohort 7: LBH 25mg + INC 15mg (Expansion Phase) N = 23**	**All Patients (MTD/RPIID) N = 34**	**Total Patients N = 61**
Arm/Group Description	Subjects were treated with panobinostat at 10 mg three times per week (TIW) every other week (QOW) and ruxolitinib 5 mg twice daily (BID)	Subjects were treated with and panobinostat at 10 mg three times per week (TIW) every other week (QOW) and ruxolitinib 10 mg twice daily (BID) on a	Subjects were treated with and panobinostat at 10 mg three times per week (TIW) every other week (QOW) and ruxolitinib 15 mg twice daily (BID) on a	Subjects were treated with panobinostat at 15 mg three times per week (TIW) every other week (QOW) ruxolitinib and 15 mg twice daily (BID) on a	Subjects were treated with panobinostat at 20 mg three times per week (TIW) every other week (QOW) and ruxolitinib 15 mg twice daily (BID) on a	Subjects were treated with ruxolitinib 15 mg twice daily (BID) and panobinostat at 25 mg three times per week (TIW) every other week (QOW) on	All patients in the Escalation phase	Subjects were treated with panobinostat at 25 mg three times per week (TIW) every other week (QOW) and ruxolitinib 15 mg twice daily (BID) for at	All Patients in the maximum tolerated dose/ recommended phase 2 dose groups	All patients in the study

	on a 28 day cycle	28 day cycle	28 day cycle	28 day cycle	28 day cycle	a 28 day cycle		least 2 cycles on a 28 day cycle		
Total participants affected	1 (20.00%)	6 (75.00%)	2 (40.00%)	5 (100.00 %)	3 (75.00%)	6 (54.55%)	23 (60.53 %)	15 (65.22 %)	21 (61.76%)	38 (62.30 %)
Blood and lymphatic system disorders										
Anaemia	0 (0.00%)	1 (12.50%)	2 (40.00%)	2 (40.00%)	0 (0.00%)	1 (9.09%)	6 (15.79%)	2 (8.70%)	3 (8.82%)	8 (13.11%)
Leukocytosis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.35%)	1 (2.94%)	1 (1.64%)
Splenic infarction	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	1 (4.35%)	1 (2.94%)	2 (3.28%)
Thrombocytopenia	0 (0.00%)	1 (12.50%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	2 (5.26%)	1 (4.35%)	1 (2.94%)	3 (4.92%)
Cardiac disorders										
Bundle branch block left	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Cardiac arrest	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.35%)	1 (2.94%)	1 (1.64%)
Cardiac failure	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.35%)	1 (2.94%)	1 (1.64%)
Myocardial infarction	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Tachycardia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Gastrointestinal disorders										
Abdominal pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	1 (9.09%)	2 (5.26%)	0 (0.00%)	1 (2.94%)	2 (3.28%)
Diarrhoea	0 (0.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	2 (5.26%)	1 (4.35%)	2 (5.88%)	3 (4.92%)

Enteritis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.35%)	1 (2.94%)	1 (1.64%)
Inguinal hernia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.35%)	1 (2.94%)	1 (1.64%)
Nausea	0 (0.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	2 (5.26%)	0 (0.00%)	1 (2.94%)	2 (3.28%)
Vomiting	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	1 (2.63%)	0 (0.00%)	1 (2.94%)	1 (1.64%)
General disorders and administration site conditions										
General physical health deterioration	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.35%)	1 (2.94%)	1 (1.64%)
Multiple organ dysfunction syndrome	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Pyrexia	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	2 (5.26%)	3 (13.04%)	3 (8.82%)	5 (8.20%)
Hepatobiliary disorders										
Cholelithiasis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	1 (2.63%)	0 (0.00%)	1 (2.94%)	1 (1.64%)
Hepatocellular injury	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.35%)	1 (2.94%)	1 (1.64%)
Hepatomegaly	0 (0.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Infections and infestations										
Abscess limb	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Atypical pneumonia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.35%)	1 (2.94%)	1 (1.64%)
Bacteraemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.35%)	1 (2.94%)	1 (1.64%)
Bronchitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.35%)	1 (2.94%)	1 (1.64%)
Cellulitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.35%)	1 (2.94%)	1 (1.64%)

Citrobacter infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.35%)	1 (2.94%)	1 (1.64%)
Device related infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Diverticulitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.35%)	1 (2.94%)	1 (1.64%)
Escherichia sepsis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Gastroenteritis	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Gingival abscess	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
H1N1 influenza	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.35%)	1 (2.94%)	1 (1.64%)
Lower respiratory tract infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.35%)	1 (2.94%)	1 (1.64%)
Pneumonia	0 (0.00%)	0 (0.00%)	1 (20.00%)	2 (40.00%)	0 (0.00%)	0 (0.00%)	3 (7.89%)	3 (13.04%)	3 (8.82%)	6 (9.84%)
Pyelonephritis	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Sepsis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (8.70%)	2 (5.88%)	2 (3.28%)
Sialoadenitis	0 (0.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Sinusitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.35%)	1 (2.94%)	1 (1.64%)
Staphylococcal sepsis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.35%)	1 (2.94%)	1 (1.64%)
Injury, poisoning and procedural complications										
Fall	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.35%)	1 (2.94%)	1 (1.64%)
Limb injury	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.35%)	1 (2.94%)	1 (1.64%)
Upper limb fracture	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Investigations										

Blood phosphorus decreased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.35%)	1 (2.94%)	1 (1.64%)
Metabolism and nutrition disorders										
Dehydration	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	1 (2.63%)	0 (0.00%)	1 (2.94%)	1 (1.64%)
Diabetes mellitus	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Hypocalcaemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.35%)	1 (2.94%)	1 (1.64%)
Musculoskeletal and connective tissue disorders										
Intervertebral disc protrusion	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	1 (2.63%)	0 (0.00%)	1 (2.94%)	1 (1.64%)
Musculoskeletal pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	1 (2.63%)	0 (0.00%)	1 (2.94%)	1 (1.64%)
Pain in extremity	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	1 (2.63%)	0 (0.00%)	1 (2.94%)	1 (1.64%)
Soft tissue necrosis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.35%)	1 (2.94%)	1 (1.64%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)										
Acute myeloid leukaemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.35%)	1 (2.94%)	1 (1.64%)
Anaplastic astrocytoma	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Basal cell carcinoma	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	1 (4.35%)	1 (2.94%)	2 (3.28%)

Bladder cancer	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Diffuse large B-cell lymphoma	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.35%)	1 (2.94%)	1 (1.64%)
Metastatic squamous cell carcinoma	0 (0.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Nasal cavity cancer	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Neoplasm	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.35%)	1 (2.94%)	1 (1.64%)
Squamous cell carcinoma	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.35%)	1 (2.94%)	1 (1.64%)
Nervous system disorders										
Aphasia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	1 (2.63%)	0 (0.00%)	1 (2.94%)	1 (1.64%)
Multiple sclerosis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.35%)	1 (2.94%)	1 (1.64%)
Sciatica	0 (0.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Transient ischaemic attack	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	1 (2.63%)	0 (0.00%)	1 (2.94%)	1 (1.64%)
Reproductive system and breast disorders										
Acquired hydrocele	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.35%)	1 (2.94%)	1 (1.64%)
Respiratory, thoracic and mediastinal disorders										
Dyspnoea	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	1 (2.63%)	0 (0.00%)	1 (2.94%)	1 (1.64%)
Pulmonary hypertension	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	1 (2.63%)	1 (4.35%)	2 (5.88%)	2 (3.28%)

Pulmonary oedema	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.35%)	1 (2.94%)	1 (1.64%)
Vascular disorders										
Hypertension	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.35%)	1 (2.94%)	1 (1.64%)

Other Adverse Events by System Organ Class

Time Frame	Adverse Events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV).
Source Vocabulary for Table Default	MedDRA (23.0)
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	5%

	Cohort 1: LBH 10mg + INC 5mg (Escalation Phase) N = 5	**Cohort 2: LBH 10mg + INC 10mg (Escalation Phase) N = 8**	**Cohort 3: LBH 10mg + INC 15mg (Escalation Phase) N = 5**	**Cohort 4: LBH 15mg + INC 15mg (Escalation Phase) N = 5**	**Cohort 5: LBH 20mg + INC 15mg (Escalation Phase) N = 4**	**Cohort 6: LBH 25mg + INC 15mg (Escalation Phase) N = 11**	**All patients (Escalation phase) N = 38**	**Cohort 7: LBH 25mg + INC 15mg (Expansion Phase) N = 23**	**All Patients (MTD/RPIID) N = 34**	**Total Patients N = 61**
Arm/Group Description	Subjects were treated with panobinostat 10 mg three times per week (TIW) every other	Subjects were treated with and panobinostat 10 mg three times per week (TIW) every other	Subjects were treated with and panobinostat 10 mg three times per week (TIW) every other	Subjects were treated with panobinostat 15 mg three times per week (TIW) every other	Subjects were treated with panobinostat 20 mg three times per week (TIW) every other	Subjects were treated with ruxolitinib 15 mg twice daily (BID) and panobinostat 25 mg three times per week	All patients in the Escalation phase	Subjects were treated with panobinostat 25 mg three times per week (TIW) every other week (QOW)	All Patients in the maximum tolerated dose/ recommended phase 2 dose groups	All patients in the study

	week (QOW) and ruxolitinib 5 mg twice daily (BID) on a 28 day cycle	week (QOW) and ruxolitinib 10 mg twice daily (BID) on a 28 day cycle	week (QOW) and ruxolitinib 15 mg twice daily (BID) on a 28 day cycle	week (QOW) ruxolitinib and 15 mg twice daily (BID) on a 28 day cycle	week (QOW) and ruxolitinib 15 mg twice daily (BID) on a 28 day cycle	(TIW) every other week (QOW) on a 28 day cycle		and ruxolitinib 15 mg twice daily (BID) for at least 2 cycles on a 28 day cycle		
Total participants affected	5 (100.00 %)	8 (100.00 %)	5 (100.00 %)	5 (100.00 %)	4 (100.00 %)	11 (100.00 %)	38 (100.00 %)	23 (100.00 %)	34 (100.00 %)	61 (100.00 %)
Blood and lymphatic system disorders										
Anaemia	2 (40.00%)	3 (37.50%)	4 (80.00%)	3 (60.00%)	3 (75.00%)	8 (72.73%)	23 (60.53 %)	21 (91.30 %)	29 (85.29%)	44 (72.13 %)
Febrile neutropenia	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Iron deficiency anaemia	0 (0.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Leukocytosis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (8.70%)	2 (5.88%)	2 (3.28%)
Leukopenia	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	2 (18.18%)	3 (7.89%)	2 (8.70%)	4 (11.76%)	5 (8.20%)
Lymphadenopathy	0 (0.00%)	0 (0.00%)	1 (20.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	2 (5.26%)	1 (4.35%)	1 (2.94%)	3 (4.92%)
Neutropenia	0 (0.00%)	0 (0.00%)	1 (20.00%)	1 (20.00%)	0 (0.00%)	3 (27.27%)	5 (13.16%)	2 (8.70%)	5 (14.71%)	7 (11.48%)
Thrombocytopenia	3 (60.00%)	4 (50.00%)	3 (60.00%)	4 (80.00%)	2 (50.00%)	6 (54.55%)	22 (57.89 %)	11 (47.83 %)	17 (50.00%)	33 (54.10 %)
Cardiac disorders										
Angina pectoris	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	1 (9.09%)	2 (5.26%)	1 (4.35%)	2 (5.88%)	3 (4.92%)

Atrial fibrillation	0 (0.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	2 (5.26%)	1 (4.35%)	2 (5.88%)	3 (4.92%)
Atrioventricular block first degree	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Bradycardia	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Cardiac failure	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	1 (4.35%)	1 (2.94%)	2 (3.28%)
Cardiac flutter	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Cardiovascular disorder	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	1 (2.63%)	0 (0.00%)	1 (2.94%)	1 (1.64%)
Coronary artery disease	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	1 (4.35%)	1 (2.94%)	2 (3.28%)
Diastolic dysfunction	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	1 (4.35%)	1 (2.94%)	2 (3.28%)
Extrasystoles	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	1 (4.35%)	1 (2.94%)	2 (3.28%)
Hypertensive heart disease	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Mitral valve incompetence	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Palpitations	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	2 (8.70%)	2 (5.88%)	3 (4.92%)
Sinus arrhythmia	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Sinus bradycardia	0 (0.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Sinus tachycardia	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	1 (4.35%)	1 (2.94%)	2 (3.28%)
Supraventricular tachycardia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)

Tachycardia	1 (20.00%)	1 (12.50%)	2 (40.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	5 (13.16%)	1 (4.35%)	1 (2.94%)	6 (9.84%)
Ventricular arrhythmia	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Ventricular extrasystoles	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Ear and labyrinth disorders										
Deafness	0 (0.00%)	0 (0.00%)	1 (20.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	2 (5.26%)	0 (0.00%)	0 (0.00%)	2 (3.28%)
Ear congestion	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Excessive cerumen production	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Hypoacusis	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	2 (5.26%)	0 (0.00%)	1 (2.94%)	2 (3.28%)
Sudden hearing loss	0 (0.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Tinnitus	0 (0.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	2 (5.26%)	0 (0.00%)	1 (2.94%)	2 (3.28%)
Endocrine disorders										
Hyperprolactinaemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Hyperthyroidism	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	1 (2.63%)	1 (4.35%)	2 (5.88%)	2 (3.28%)
Hypothyroidism	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	2 (5.26%)	2 (8.70%)	2 (5.88%)	4 (6.56%)
Eye disorders										
Blepharitis	0 (0.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)

Blindness	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	1 (9.09%)	2 (5.26%)	0 (0.00%)	1 (2.94%)	2 (3.28%)
Cataract	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (18.18%)	2 (5.26%)	2 (8.70%)	4 (11.76%)	4 (6.56%)
Chalazion	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	1 (2.63%)	1 (4.35%)	2 (5.88%)	2 (3.28%)
Conjunctival haemorrhage	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	1 (4.35%)	1 (2.94%)	2 (3.28%)
Conjunctival irritation	0 (0.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Conjunctival oedema	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	1 (2.63%)	0 (0.00%)	1 (2.94%)	1 (1.64%)
Dry eye	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	1 (4.35%)	1 (2.94%)	2 (3.28%)
Eye haemorrhage	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (8.70%)	2 (5.88%)	2 (3.28%)
Eye pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	2 (18.18%)	3 (7.89%)	0 (0.00%)	2 (5.88%)	3 (4.92%)
Eye pruritus	0 (0.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	2 (5.26%)	2 (8.70%)	3 (8.82%)	4 (6.56%)
Foreign body sensation in eyes	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Periorbital pain	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Photopsia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	1 (2.63%)	0 (0.00%)	1 (2.94%)	1 (1.64%)
Retinal haemorrhage	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	1 (9.09%)	2 (5.26%)	1 (4.35%)	2 (5.88%)	3 (4.92%)
Vision blurred	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	1 (2.63%)	1 (4.35%)	2 (5.88%)	2 (3.28%)
Vitreous detachment	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	1 (2.63%)	0 (0.00%)	1 (2.94%)	1 (1.64%)
Gastrointestinal disorders										

Abdominal discomfort	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	1 (9.09%)	2 (5.26%)	2 (8.70%)	3 (8.82%)	4 (6.56%)
Abdominal distension	0 (0.00%)	2 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (18.18%)	4 (10.53%)	0 (0.00%)	2 (5.88%)	4 (6.56%)
Abdominal pain	2 (40.00%)	2 (25.00%)	2 (40.00%)	0 (0.00%)	1 (25.00%)	3 (27.27%)	10 (26.32%)	7 (30.43%)	10 (29.41%)	17 (27.87%)
Abdominal pain upper	3 (60.00%)	0 (0.00%)	1 (20.00%)	1 (20.00%)	0 (0.00%)	3 (27.27%)	8 (21.05%)	2 (8.70%)	5 (14.71%)	10 (16.39%)
Abdominal tenderness	0 (0.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Anal fissure	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	1 (2.63%)	0 (0.00%)	1 (2.94%)	1 (1.64%)
Aphthous ulcer	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	1 (2.63%)	3 (13.04%)	4 (11.76%)	4 (6.56%)
Ascites	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	1 (4.35%)	1 (2.94%)	2 (3.28%)
Constipation	1 (20.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (27.27%)	5 (13.16%)	4 (17.39%)	7 (20.59%)	9 (14.75%)
Dental caries	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (13.04%)	3 (8.82%)	3 (4.92%)
Diarrhoea	3 (60.00%)	4 (50.00%)	5 (100.00%)	3 (60.00%)	1 (25.00%)	9 (81.82%)	25 (65.79%)	17 (73.91%)	26 (76.47%)	42 (68.85%)
Dry mouth	1 (20.00%)	0 (0.00%)	0 (0.00%)	2 (40.00%)	0 (0.00%)	1 (9.09%)	4 (10.53%)	1 (4.35%)	2 (5.88%)	5 (8.20%)
Dyspepsia	1 (20.00%)	2 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	4 (10.53%)	0 (0.00%)	1 (2.94%)	4 (6.56%)
Dysphagia	0 (0.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	1 (4.35%)	1 (2.94%)	2 (3.28%)
Flatulence	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	2 (8.70%)	2 (5.88%)	3 (4.92%)
Gastritis	0 (0.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Gastrooesophageal reflux disease	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	1 (2.63%)	1 (4.35%)	2 (5.88%)	2 (3.28%)

Gingival bleeding	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	2 (8.70%)	2 (5.88%)	3 (4.92%)
Gingival pain	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Haematochezia	0 (0.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (18.18%)	3 (7.89%)	0 (0.00%)	2 (5.88%)	3 (4.92%)
Haemorrhoids	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	1 (2.63%)	1 (4.35%)	2 (5.88%)	2 (3.28%)
Irritable bowel syndrome	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Large intestine polyp	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	1 (2.63%)	0 (0.00%)	1 (2.94%)	1 (1.64%)
Mouth ulceration	2 (40.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (7.89%)	1 (4.35%)	1 (2.94%)	4 (6.56%)
Nausea	1 (20.00%)	3 (37.50%)	2 (40.00%)	2 (40.00%)	0 (0.00%)	6 (54.55%)	14 (36.84%)	7 (30.43%)	13 (38.24%)	21 (34.43%)
Oesophageal ulcer	0 (0.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Oesophagitis	0 (0.00%)	2 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (5.26%)	0 (0.00%)	0 (0.00%)	2 (3.28%)
Rectal haemorrhage	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Salivary gland disorder	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	1 (2.63%)	0 (0.00%)	1 (2.94%)	1 (1.64%)
Stomatitis	1 (20.00%)	0 (0.00%)	1 (20.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	3 (7.89%)	1 (4.35%)	1 (2.94%)	4 (6.56%)
Tooth loss	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	1 (4.35%)	1 (2.94%)	2 (3.28%)
Toothache	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	2 (5.26%)	0 (0.00%)	1 (2.94%)	2 (3.28%)
Upper gastrointestinal haemorrhage	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	1 (2.63%)	0 (0.00%)	1 (2.94%)	1 (1.64%)

Vomiting	1 (20.00%)	2 (25.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	7 (63.64%)	11 (28.95%)	7 (30.43%)	14 (41.18%)	18 (29.51%)
General disorders and administration site conditions										
Asthenia	0 (0.00%)	2 (25.00%)	3 (60.00%)	3 (60.00%)	1 (25.00%)	7 (63.64%)	16 (42.11%)	11 (47.83%)	18 (52.94%)	27 (44.26%)
Chest pain	0 (0.00%)	1 (12.50%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (5.26%)	0 (0.00%)	0 (0.00%)	2 (3.28%)
Chills	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Fatigue	1 (20.00%)	2 (25.00%)	1 (20.00%)	0 (0.00%)	1 (25.00%)	4 (36.36%)	9 (23.68%)	7 (30.43%)	11 (32.35%)	16 (26.23%)
Feeling cold	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	1 (2.63%)	1 (4.35%)	2 (5.88%)	2 (3.28%)
Feeling hot	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	1 (2.63%)	0 (0.00%)	1 (2.94%)	1 (1.64%)
Gait disturbance	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
General physical health deterioration	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Influenza like illness	1 (20.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (5.26%)	2 (8.70%)	2 (5.88%)	4 (6.56%)
Injection site pain	0 (0.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Malaise	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	1 (2.63%)	1 (4.35%)	2 (5.88%)	2 (3.28%)
Mass	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Medical device pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Nodule	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)

Non-cardiac chest pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	1 (9.09%)	2 (5.26%)	2 (8.70%)	3 (8.82%)	4 (6.56%)
Oedema	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	1 (2.63%)	0 (0.00%)	1 (2.94%)	1 (1.64%)
Oedema peripheral	1 (20.00%)	2 (25.00%)	2 (40.00%)	3 (60.00%)	2 (50.00%)	4 (36.36%)	14 (36.84%)	9 (39.13%)	13 (38.24%)	23 (37.70%)
Pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	1 (2.63%)	3 (13.04%)	4 (11.76%)	4 (6.56%)
Peripheral swelling	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	1 (4.35%)	1 (2.94%)	2 (3.28%)
Pyrexia	0 (0.00%)	1 (12.50%)	2 (40.00%)	1 (20.00%)	0 (0.00%)	4 (36.36%)	8 (21.05%)	7 (30.43%)	11 (32.35%)	15 (24.59%)
Temperature intolerance	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	1 (2.63%)	0 (0.00%)	1 (2.94%)	1 (1.64%)
Xerosis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	1 (2.63%)	0 (0.00%)	1 (2.94%)	1 (1.64%)
Hepatobiliary disorders										
Hepatic steatosis	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Hepatic vein thrombosis	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Hepatocellular injury	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Hepatomegaly	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Hyperbilirubinaemia	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Immune system disorders										
Drug hypersensitivity	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	1 (2.63%)	1 (4.35%)	2 (5.88%)	2 (3.28%)
Infections and infestations										

Blister infected	0 (0.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Bronchitis	1 (20.00%)	3 (37.50%)	1 (20.00%)	1 (20.00%)	1 (25.00%)	2 (18.18%)	9 (23.68%)	3 (13.04%)	5 (14.71%)	12 (19.67%)
Conjunctivitis	0 (0.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Cystitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	2 (18.18%)	3 (7.89%)	1 (4.35%)	3 (8.82%)	4 (6.56%)
Dysentery	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (8.70%)	2 (5.88%)	2 (3.28%)
Ear infection	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Enterococcal infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Epididymitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Epstein-Barr virus infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	1 (2.63%)	1 (4.35%)	2 (5.88%)	2 (3.28%)
Gastroenteritis	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	1 (9.09%)	2 (5.26%)	1 (4.35%)	2 (5.88%)	3 (4.92%)
Gingival abscess	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Herpes simplex	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	1 (9.09%)	2 (5.26%)	1 (4.35%)	2 (5.88%)	3 (4.92%)
Herpes virus infection	0 (0.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	2 (5.26%)	0 (0.00%)	1 (2.94%)	2 (3.28%)
Herpes zoster	0 (0.00%)	2 (25.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	1 (9.09%)	4 (10.53%)	1 (4.35%)	2 (5.88%)	5 (8.20%)
Hordeolum	0 (0.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	2 (5.26%)	0 (0.00%)	1 (2.94%)	2 (3.28%)
Influenza	0 (0.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	3 (27.27%)	5 (13.16%)	3 (13.04%)	6 (17.65%)	8 (13.11%)

Lower respiratory tract infection	1 (20.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	3 (7.89%)	4 (17.39%)	5 (14.71%)	7 (11.48%)
Lower respiratory tract infection viral	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Nasopharyngitis	1 (20.00%)	3 (37.50%)	1 (20.00%)	1 (20.00%)	0 (0.00%)	1 (9.09%)	7 (18.42%)	6 (26.09%)	7 (20.59%)	13 (21.31%)
Onychomycosis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	1 (2.63%)	0 (0.00%)	1 (2.94%)	1 (1.64%)
Oral herpes	1 (20.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (18.18%)	4 (10.53%)	3 (13.04%)	5 (14.71%)	7 (11.48%)
Otitis externa	0 (0.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Paronychia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	1 (2.63%)	0 (0.00%)	1 (2.94%)	1 (1.64%)
Parotitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Pharyngitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	1 (2.63%)	1 (4.35%)	2 (5.88%)	2 (3.28%)
Pneumonia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	1 (2.63%)	2 (8.70%)	2 (5.88%)	3 (4.92%)
Post procedural infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	1 (2.63%)	0 (0.00%)	1 (2.94%)	1 (1.64%)
Prostate infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	1 (2.63%)	0 (0.00%)	1 (2.94%)	1 (1.64%)
Respiratory tract infection	0 (0.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	1 (4.35%)	1 (2.94%)	2 (3.28%)
Rhinitis	0 (0.00%)	3 (37.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (18.18%)	5 (13.16%)	0 (0.00%)	2 (5.88%)	5 (8.20%)
Sinusitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (27.27%)	3 (7.89%)	0 (0.00%)	3 (8.82%)	3 (4.92%)
Soft tissue infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	1 (2.63%)	0 (0.00%)	1 (2.94%)	1 (1.64%)
Staphylococcal infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	1 (25.00%)	0 (0.00%)	2 (5.26%)	0 (0.00%)	0 (0.00%)	2 (3.28%)

Tooth infection	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	1 (4.35%)	1 (2.94%)	2 (3.28%)
Tracheitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	1 (9.09%)	2 (5.26%)	0 (0.00%)	1 (2.94%)	2 (3.28%)
Upper respiratory tract infection	0 (0.00%)	1 (12.50%)	3 (60.00%)	0 (0.00%)	0 (0.00%)	2 (18.18%)	6 (15.79%)	3 (13.04%)	5 (14.71%)	9 (14.75%)
Urinary tract infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	1 (2.63%)	2 (8.70%)	3 (8.82%)	3 (4.92%)
Vulvovaginal candidiasis	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Yersinia infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	1 (2.63%)	0 (0.00%)	1 (2.94%)	1 (1.64%)
Injury, poisoning and procedural complications										
Conjunctival laceration	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Contusion	1 (20.00%)	1 (12.50%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	2 (18.18%)	5 (13.16%)	4 (17.39%)	6 (17.65%)	9 (14.75%)
Craniocerebral injury	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Eye contusion	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Eye injury	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Eyelid contusion	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Fall	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	3 (13.04%)	3 (8.82%)	4 (6.56%)
Ligament sprain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	1 (2.63%)	2 (8.70%)	3 (8.82%)	3 (4.92%)
Muscle rupture	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	1 (2.63%)	0 (0.00%)	1 (2.94%)	1 (1.64%)
Muscle strain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	1 (2.63%)	0 (0.00%)	1 (2.94%)	1 (1.64%)

Nasal injury	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Scapula fracture	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Skin abrasion	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	1 (2.63%)	0 (0.00%)	1 (2.94%)	1 (1.64%)
Skin laceration	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (8.70%)	2 (5.88%)	2 (3.28%)
Tooth fracture	0 (0.00%)	0 (0.00%)	2 (40.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (5.26%)	0 (0.00%)	0 (0.00%)	2 (3.28%)
Investigations										
Alanine aminotransferase increased	2 (40.00%)	1 (12.50%)	1 (20.00%)	0 (0.00%)	1 (25.00%)	1 (9.09%)	6 (15.79%)	1 (4.35%)	2 (5.88%)	7 (11.48%)
Aspartate aminotransferase increased	2 (40.00%)	1 (12.50%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	5 (13.16%)	0 (0.00%)	1 (2.94%)	5 (8.20%)
Blast cell count increased	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Blood alkaline phosphatase increased	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	2 (5.26%)	2 (8.70%)	2 (5.88%)	4 (6.56%)
Blood bilirubin increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	1 (9.09%)	2 (5.26%)	0 (0.00%)	1 (2.94%)	2 (3.28%)
Blood creatine phosphokinase increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (18.18%)	2 (5.26%)	2 (8.70%)	4 (11.76%)	4 (6.56%)
Blood creatinine increased	1 (20.00%)	3 (37.50%)	1 (20.00%)	1 (20.00%)	2 (50.00%)	3 (27.27%)	11 (28.95%)	4 (17.39%)	7 (20.59%)	15 (24.59%)
Blood lactate dehydrogenase increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	1 (2.63%)	1 (4.35%)	2 (5.88%)	2 (3.28%)
Blood pressure decreased	0 (0.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)

Blood pressure increased	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Blood urea increased	0 (0.00%)	2 (25.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	3 (7.89%)	0 (0.00%)	0 (0.00%)	3 (4.92%)
Blood uric acid increased	2 (40.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (50.00%)	0 (0.00%)	4 (10.53%)	0 (0.00%)	0 (0.00%)	4 (6.56%)
Cardiac murmur	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (50.00%)	0 (0.00%)	3 (7.89%)	0 (0.00%)	0 (0.00%)	3 (4.92%)
Electrocardiogram QT prolonged	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	1 (2.63%)	2 (8.70%)	3 (8.82%)	3 (4.92%)
Electrocardiogram T wave inversion	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (8.70%)	2 (5.88%)	2 (3.28%)
Gamma-glutamyltransferase increased	2 (40.00%)	1 (12.50%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	4 (10.53%)	1 (4.35%)	1 (2.94%)	5 (8.20%)
Haematocrit increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	1 (2.63%)	0 (0.00%)	1 (2.94%)	1 (1.64%)
Haemoglobin decreased	0 (0.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	2 (5.26%)	0 (0.00%)	1 (2.94%)	2 (3.28%)
Heart rate increased	0 (0.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
International normalised ratio increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
N-terminal prohormone brain natriuretic peptide increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Platelet count decreased	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	1 (25.00%)	1 (9.09%)	3 (7.89%)	5 (21.74%)	6 (17.65%)	8 (13.11%)
QRS axis abnormal	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)

Renal function test abnormal	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	1 (2.63%)	0 (0.00%)	1 (2.94%)	1 (1.64%)
Serum ferritin increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	1 (2.63%)	1 (4.35%)	2 (5.88%)	2 (3.28%)
Transaminases increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Weight decreased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	1 (9.09%)	2 (5.26%)	1 (4.35%)	2 (5.88%)	3 (4.92%)
Weight increased	0 (0.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	2 (5.26%)	5 (21.74%)	6 (17.65%)	7 (11.48%)
Metabolism and nutrition disorders										
Decreased appetite	0 (0.00%)	0 (0.00%)	2 (40.00%)	1 (20.00%)	0 (0.00%)	5 (45.45%)	8 (21.05%)	3 (13.04%)	8 (23.53%)	11 (18.03%)
Diabetes mellitus	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Fluid retention	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (8.70%)	2 (5.88%)	2 (3.28%)
Folate deficiency	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Gout	0 (0.00%)	1 (12.50%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (5.26%)	1 (4.35%)	1 (2.94%)	3 (4.92%)
Hypercholesterolaemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	1 (2.63%)	0 (0.00%)	1 (2.94%)	1 (1.64%)
Hyperglycaemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	1 (2.63%)	0 (0.00%)	1 (2.94%)	1 (1.64%)
Hyperkalaemia	0 (0.00%)	1 (12.50%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	2 (18.18%)	4 (10.53%)	4 (17.39%)	6 (17.65%)	8 (13.11%)
Hyperphosphataemia	0 (0.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	2 (8.70%)	2 (5.88%)	3 (4.92%)
Hypertriglyceridaemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	1 (2.63%)	0 (0.00%)	1 (2.94%)	1 (1.64%)

Hyperuricaemia	0 (0.00%)	1 (12.50%)	1 (20.00%)	0 (0.00%)	1 (25.00%)	1 (9.09%)	4 (10.53%)	1 (4.35%)	2 (5.88%)	5 (8.20%)
Hypocalcaemia	0 (0.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (18.18%)	3 (7.89%)	3 (13.04%)	5 (14.71%)	6 (9.84%)
Hypokalaemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	1 (9.09%)	2 (5.26%)	1 (4.35%)	2 (5.88%)	3 (4.92%)
Hypomagnesaemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	1 (2.63%)	0 (0.00%)	1 (2.94%)	1 (1.64%)
Iron deficiency	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Iron overload	0 (0.00%)	1 (12.50%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	3 (7.89%)	0 (0.00%)	1 (2.94%)	3 (4.92%)
Type 2 diabetes mellitus	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Vitamin B12 deficiency	0 (0.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Vitamin D deficiency	1 (20.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (5.26%)	0 (0.00%)	0 (0.00%)	2 (3.28%)
Musculoskeletal and connective tissue disorders										
Arthralgia	1 (20.00%)	2 (25.00%)	2 (40.00%)	2 (40.00%)	0 (0.00%)	4 (36.36%)	11 (28.95%)	4 (17.39%)	8 (23.53%)	15 (24.59%)
Back pain	3 (60.00%)	0 (0.00%)	1 (20.00%)	1 (20.00%)	0 (0.00%)	4 (36.36%)	9 (23.68%)	6 (26.09%)	10 (29.41%)	15 (24.59%)
Bone pain	1 (20.00%)	2 (25.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	1 (9.09%)	5 (13.16%)	2 (8.70%)	3 (8.82%)	7 (11.48%)
Dupuytren's contracture	0 (0.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Groin pain	0 (0.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	1 (4.35%)	1 (2.94%)	2 (3.28%)

Intervertebral disc protrusion	0 (0.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Joint swelling	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	1 (9.09%)	2 (5.26%)	2 (8.70%)	3 (8.82%)	4 (6.56%)
Muscle spasms	2 (40.00%)	3 (37.50%)	2 (40.00%)	2 (40.00%)	0 (0.00%)	5 (45.45%)	14 (36.84%)	8 (34.78%)	13 (38.24%)	22 (36.07%)
Muscular weakness	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	1 (2.63%)	1 (4.35%)	2 (5.88%)	2 (3.28%)
Musculoskeletal chest pain	0 (0.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	2 (5.26%)	0 (0.00%)	1 (2.94%)	2 (3.28%)
Musculoskeletal pain	2 (40.00%)	2 (25.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	5 (13.16%)	1 (4.35%)	1 (2.94%)	6 (9.84%)
Myalgia	1 (20.00%)	1 (12.50%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	1 (9.09%)	4 (10.53%)	2 (8.70%)	3 (8.82%)	6 (9.84%)
Neck pain	0 (0.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	2 (5.26%)	0 (0.00%)	1 (2.94%)	2 (3.28%)
Osteoarthritis	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	1 (4.35%)	1 (2.94%)	2 (3.28%)
Osteoarthropathy	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Pain in extremity	2 (40.00%)	1 (12.50%)	1 (20.00%)	1 (20.00%)	0 (0.00%)	4 (36.36%)	9 (23.68%)	6 (26.09%)	10 (29.41%)	15 (24.59%)
Periarthritis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	1 (2.63%)	1 (4.35%)	2 (5.88%)	2 (3.28%)
Plantar fascial fibromatosis	0 (0.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Spinal pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	1 (2.63%)	1 (4.35%)	2 (5.88%)	2 (3.28%)
Synovitis	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)										

Basal cell carcinoma	0 (0.00%)	1 (12.50%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	3 (7.89%)	1 (4.35%)	2 (5.88%)	4 (6.56%)
Bladder papilloma	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Bowen's disease	0 (0.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Gastrointestinal tract adenoma	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	1 (2.63%)	0 (0.00%)	1 (2.94%)	1 (1.64%)
Haemangioma	0 (0.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Melanocytic naevus	0 (0.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Monoclonal gammopathy	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Nasal cavity cancer	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Nasal neoplasm	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Prostate cancer	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	1 (2.63%)	0 (0.00%)	1 (2.94%)	1 (1.64%)
Skin papilloma	0 (0.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Squamous cell carcinoma	0 (0.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	1 (4.35%)	1 (2.94%)	2 (3.28%)
Squamous cell carcinoma of skin	0 (0.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	2 (8.70%)	2 (5.88%)	3 (4.92%)
Transitional cell carcinoma	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Nervous system disorders										
Ageusia	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	2 (5.26%)	0 (0.00%)	1 (2.94%)	2 (3.28%)

Amnesia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	1 (2.63%)	0 (0.00%)	1 (2.94%)	1 (1.64%)
Aphasia	0 (0.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Balance disorder	1 (20.00%)	0 (0.00%)	1 (20.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	3 (7.89%)	1 (4.35%)	1 (2.94%)	4 (6.56%)
Burning sensation	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	1 (4.35%)	1 (2.94%)	2 (3.28%)
Carotid arteriosclerosis	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Cerebrovascular accident	0 (0.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Disturbance in attention	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	1 (9.09%)	2 (5.26%)	0 (0.00%)	1 (2.94%)	2 (3.28%)
Dizziness	2 (40.00%)	2 (25.00%)	2 (40.00%)	0 (0.00%)	0 (0.00%)	5 (45.45%)	11 (28.95%)	4 (17.39%)	9 (26.47%)	15 (24.59%)
Dizziness postural	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Dysarthria	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Dysgeusia	0 (0.00%)	1 (12.50%)	1 (20.00%)	1 (20.00%)	0 (0.00%)	2 (18.18%)	5 (13.16%)	0 (0.00%)	2 (5.88%)	5 (8.20%)
Dyskinesia	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Extrapyramidal disorder	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Headache	1 (20.00%)	3 (37.50%)	2 (40.00%)	1 (20.00%)	1 (25.00%)	5 (45.45%)	13 (34.21%)	7 (30.43%)	12 (35.29%)	20 (32.79%)
Hemiparesis	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Hypoaesthesia	0 (0.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	1 (4.35%)	1 (2.94%)	2 (3.28%)

Hypoglossal nerve paralysis	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Hyposmia	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Lethargy	0 (0.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	1 (4.35%)	1 (2.94%)	2 (3.28%)
Leukoencephalopathy	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Memory impairment	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Neuralgia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (18.18%)	2 (5.26%)	0 (0.00%)	2 (5.88%)	2 (3.28%)
Neuropathy peripheral	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Paraesthesia	0 (0.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	2 (5.26%)	1 (4.35%)	2 (5.88%)	3 (4.92%)
Peripheral sensory neuropathy	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (8.70%)	2 (5.88%)	2 (3.28%)
Sciatica	0 (0.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (18.18%)	3 (7.89%)	0 (0.00%)	2 (5.88%)	3 (4.92%)
Sensorimotor disorder	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Sensory disturbance	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	1 (2.63%)	0 (0.00%)	1 (2.94%)	1 (1.64%)
Sensory loss	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	1 (2.63%)	0 (0.00%)	1 (2.94%)	1 (1.64%)
Sinus headache	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	1 (2.63%)	0 (0.00%)	1 (2.94%)	1 (1.64%)
Somnolence	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	1 (9.09%)	2 (5.26%)	0 (0.00%)	1 (2.94%)	2 (3.28%)
Speech disorder	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Syncope	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	1 (2.63%)	0 (0.00%)	1 (2.94%)	1 (1.64%)

Taste disorder	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	1 (2.63%)	1 (4.35%)	2 (5.88%)	2 (3.28%)
Transient ischaemic attack	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Tremor	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	2 (5.26%)	0 (0.00%)	0 (0.00%)	2 (3.28%)
Psychiatric disorders										
Abnormal dreams	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	1 (2.63%)	0 (0.00%)	1 (2.94%)	1 (1.64%)
Anxiety	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	1 (2.63%)	0 (0.00%)	1 (2.94%)	1 (1.64%)
Bulimia nervosa	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Confusional state	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (18.18%)	2 (5.26%)	0 (0.00%)	2 (5.88%)	2 (3.28%)
Depressed mood	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	1 (4.35%)	1 (2.94%)	2 (3.28%)
Depression	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	1 (9.09%)	2 (5.26%)	1 (4.35%)	2 (5.88%)	3 (4.92%)
Disorientation	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Hallucination	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Insomnia	0 (0.00%)	1 (12.50%)	1 (20.00%)	2 (40.00%)	0 (0.00%)	3 (27.27%)	7 (18.42%)	0 (0.00%)	3 (8.82%)	7 (11.48%)
Mood altered	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	1 (2.63%)	1 (4.35%)	2 (5.88%)	2 (3.28%)
Sleep disorder	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	1 (2.63%)	1 (4.35%)	2 (5.88%)	2 (3.28%)
Renal and urinary disorders										
Dysuria	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	1 (2.63%)	0 (0.00%)	1 (2.94%)	1 (1.64%)
Haematuria	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)

Micturition urgency	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	1 (2.63%)	0 (0.00%)	1 (2.94%)	1 (1.64%)
Nocturia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (18.18%)	2 (5.26%)	0 (0.00%)	2 (5.88%)	2 (3.28%)
Pollakiuria	2 (40.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	1 (9.09%)	4 (10.53%)	2 (8.70%)	3 (8.82%)	6 (9.84%)
Proteinuria	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	1 (4.35%)	1 (2.94%)	2 (3.28%)
Renal failure	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (18.18%)	2 (5.26%)	1 (4.35%)	3 (8.82%)	3 (4.92%)
Renal impairment	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	2 (8.70%)	2 (5.88%)	3 (4.92%)
Urinary retention	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	1 (2.63%)	0 (0.00%)	1 (2.94%)	1 (1.64%)
Reproductive system and breast disorders										
Benign prostatic hyperplasia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Breast pain	0 (0.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Endometrial hyperplasia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	1 (2.63%)	0 (0.00%)	1 (2.94%)	1 (1.64%)
Prostatic pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Prostatitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	1 (4.35%)	1 (2.94%)	2 (3.28%)
Vaginal discharge	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	1 (2.63%)	1 (4.35%)	2 (5.88%)	2 (3.28%)
Respiratory, thoracic and mediastinal disorders										
Cough	1 (20.00%)	3 (37.50%)	3 (60.00%)	1 (20.00%)	1 (25.00%)	3 (27.27%)	12 (31.58%)	11 (47.83%)	14 (41.18%)	23 (37.70%)

Dry throat	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	1 (2.63%)	0 (0.00%)	1 (2.94%)	1 (1.64%)
Dysphonia	1 (20.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (5.26%)	0 (0.00%)	0 (0.00%)	2 (3.28%)
Dyspnoea	1 (20.00%)	1 (12.50%)	2 (40.00%)	1 (20.00%)	1 (25.00%)	6 (54.55%)	12 (31.58%)	5 (21.74%)	11 (32.35%)	17 (27.87%)
Dyspnoea exertional	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	1 (4.35%)	1 (2.94%)	2 (3.28%)
Epistaxis	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	1 (25.00%)	2 (18.18%)	4 (10.53%)	4 (17.39%)	6 (17.65%)	8 (13.11%)
Oropharyngeal pain	1 (20.00%)	1 (12.50%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	4 (10.53%)	5 (21.74%)	6 (17.65%)	9 (14.75%)
Pharyngeal erythema	0 (0.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Pleural effusion	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Productive cough	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Rales	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Rhinalgia	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Sinus pain	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Upper-airway cough syndrome	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Skin and subcutaneous tissue disorders										
Acne	0 (0.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Actinic keratosis	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	1 (9.09%)	2 (5.26%)	0 (0.00%)	1 (2.94%)	2 (3.28%)

Alopecia	1 (20.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	3 (7.89%)	2 (8.70%)	3 (8.82%)	5 (8.20%)
Aquagenic pruritus	1 (20.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (5.26%)	1 (4.35%)	1 (2.94%)	3 (4.92%)
Blister	0 (0.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Blood blister	0 (0.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Cold sweat	0 (0.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Dermal cyst	0 (0.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Dermatitis	0 (0.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Dermatitis acneiform	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	1 (2.63%)	0 (0.00%)	1 (2.94%)	1 (1.64%)
Dry skin	0 (0.00%)	1 (12.50%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	5 (45.45%)	7 (18.42%)	2 (8.70%)	7 (20.59%)	9 (14.75%)
Ecchymosis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	1 (2.63%)	1 (4.35%)	2 (5.88%)	2 (3.28%)
Eczema	0 (0.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	1 (4.35%)	1 (2.94%)	2 (3.28%)
Erythema	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	1 (2.63%)	3 (13.04%)	4 (11.76%)	4 (6.56%)
Hyperhidrosis	1 (20.00%)	0 (0.00%)	0 (0.00%)	2 (40.00%)	0 (0.00%)	1 (9.09%)	4 (10.53%)	0 (0.00%)	1 (2.94%)	4 (6.56%)
Hyperkeratosis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	1 (2.63%)	0 (0.00%)	1 (2.94%)	1 (1.64%)
Intertrigo	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	1 (2.63%)	0 (0.00%)	1 (2.94%)	1 (1.64%)
Nail dystrophy	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Night sweats	1 (20.00%)	0 (0.00%)	1 (20.00%)	1 (20.00%)	1 (25.00%)	4 (36.36%)	8 (21.05%)	5 (21.74%)	9 (26.47%)	13 (21.31%)

Onychoclasis	0 (0.00%)	1 (12.50%)	1 (20.00%)	1 (20.00%)	0 (0.00%)	1 (9.09%)	4 (10.53%)	3 (13.04%)	4 (11.76%)	7 (11.48%)
Pruritus	3 (60.00%)	3 (37.50%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	2 (18.18%)	9 (23.68%)	5 (21.74%)	7 (20.59%)	14 (22.95%)
Psoriasis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	1 (2.63%)	0 (0.00%)	1 (2.94%)	1 (1.64%)
Rash	1 (20.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	3 (7.89%)	2 (8.70%)	2 (5.88%)	5 (8.20%)
Skin haemorrhage	0 (0.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Skin lesion	0 (0.00%)	1 (12.50%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	2 (5.26%)	1 (4.35%)	1 (2.94%)	3 (4.92%)
Skin reaction	0 (0.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Skin ulcer	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	1 (2.63%)	0 (0.00%)	1 (2.94%)	1 (1.64%)
Telangiectasia	0 (0.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Vascular disorders										
Deep vein thrombosis	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)
Haematoma	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	1 (9.09%)	2 (5.26%)	1 (4.35%)	2 (5.88%)	3 (4.92%)
Hot flush	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (18.18%)	2 (5.26%)	1 (4.35%)	3 (8.82%)	3 (4.92%)
Hypertension	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (60.00%)	1 (25.00%)	1 (9.09%)	5 (13.16%)	1 (4.35%)	2 (5.88%)	6 (9.84%)
Hypotension	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	1 (2.63%)	0 (0.00%)	1 (2.94%)	1 (1.64%)
Pallor	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (8.70%)	2 (5.88%)	2 (3.28%)
Peripheral arterial occlusive disease	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	1 (2.63%)	0 (0.00%)	1 (2.94%)	1 (1.64%)
Phlebitis	0 (0.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	2 (8.70%)	2 (5.88%)	3 (4.92%)

Thrombophlebitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (1.64%)

Conclusion:

The combination of panobinostat (LBH) 25 mg three times per week every other week with ruxolitinib (INC) 15 mg twice per day is safe and tolerable for the treatment of subjects with myelofibrosis. The promising efficacy findings of this combination treatment, such as spleen size reduction, still needs to be confirmed.

Date of Clinical Trial Report

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