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Clinical Trial Results Website

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Novartis Pharmaceuticals

Generic Drug Name

PIM447, ruxolitinib (INC424) and ribociclib (LEE011)

Trial Indication(s)

myelofibrosis

Protocol Number

CPIM447X2104C

Protocol Title

A phase Ib, multi-center, open-label, dose-escalation study of PIM447 in combination with ruxolitinib (INC424) and LEE011 administered orally in patients with myelofibrosis

Clinical Trial Phase

Phase 1

Phase of Drug Development

Phase Ib

Study Start/End Dates

Study Start Date: 21 May 2015 (Actual)
Primary Completion Date: 9 November 2020 (Actual)
Study Completion Date: 9 November 2020 (Actual)

Reason for Termination (If applicable)

This study was terminated early after 15 patients were recruited in the dose escalation portion of the study due to factors including unfavorable hematologic toxicity and challenges in recruitment.

Study Design/Methodology

This was a Phase Ib, multi-center, open-label, dose-escalation study to estimate the Maximum tolerated dose (MTD) and/or Recommended dose for expansion (RDE) in three treatment arms: PIM447 plus ruxolitinib, LEE011 plus ruxolitinib, and the triple combination of PIM447 plus ruxolitinib and LEE011, in patients with Myelofibrosis (MF).

Initial dosing information in the 3 treatment arms was:

- PIM447 plus ruxolitinib: The starting dose was PIM447 150 mg q.d. and ruxolitinib 5 mg b.i.d.
- LEE011 plus ruxolitinib: The starting dose was LEE011 200 mg q.d. and ruxolitinib 5 mg b.i.d.
- PIM447, ruxolitinib, and LEE011: PIM447 150 mg q.d., ruxolitinib 5 mg b.i.d., and LEE011 100 mg q.d (provisional starting dose). Actual starting dose was determined using the most recent data from the doublet regimen, as well as Bayesian logistic regression model (BLRM) results at the time the triple combination was initiated.

PIM447 plus ruxolitinib and LEE011 plus ruxolitinib were opened in parallel followed by initiation of PIM447, ruxolitinib, and LEE011. PIM447, ruxolitinib, and LEE011 (triple combination) was initiated following Novartis and Investigator's review of the available safety, tolerability, PK and pharmacodynamics data, and preliminary anti-myelofibrosis activity of PIM447 plus ruxolitinib and LEE011 plus ruxolitinib. Dose levels were explored following the recommendations made by Bayesian logistic regression model (BLRM) with escalation with overdose control (EWOC) principle.

The Maximum tolerated dose (MTD) and or Recommended dose for expansion (RDE) was to be evaluated for each of the treatment arms. Cohorts could be added at any dose level below the MTD to understand the safety, Pharmacokinetic(s) (PK), pharmacodynamics, or clinical activity. Dose escalation were to continue until MTD/RDE had been determined for each treatment arm. Following the determination of the MTD and/or RDE for a treatment arm, an expansion cohort was

planned to enroll patients for that treatment arm to further characterize safety, tolerability, PK and pharmacodynamics, and assess preliminary anti-myelofibrosis activity.

However, the dose expansion part was not opened as the study was early terminated due to factors including unfavorable hematologic toxicity and challenges in recruitment.

Centers

9 centers in 8 countries: Australia(1), Singapore(1), Canada(1), United Kingdom(1), Italy(1), Germany(2), France(1), Netherlands(1)

Objectives:

The primary objective was to estimate the maximum tolerated dose (MTD) and/or recommended dose for expansion (RDE) for each of the following three treatment arms in patients with myelofibrosis (MF).

- PIM447 plus ruxolitinib (doublet)
- LEE011 plus ruxolitinib (doublet)
- PIM447 plus ruxolitinib and LEE 011 (triple combination)

The secondary objectives were to characterize the safety and tolerability of PIM447 plus ruxolitinib, LEE011 plus ruxolitinib, and the triple combination PIM447 plus ruxolitinib and LEE011; To assess preliminary anti-myelofibrosis activity of PIM447 plus ruxolitinib, LEE011 plus ruxolitinib, and the triple combination PIM447 plus ruxolitinib and LEE011; and to characterize the pharmacokinetic (PK) profiles of combinations of PIM447, ruxolitinib, and LEE011.

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

PIM447 and LEE011 as 50 mg and 200 mg hard gel capsules and ruxolitinib commercially available as 5 mg, 10 mg, 15 mg, and 20 mg tablets, for oral administration.

Statistical Methods

Analysis of primary variable:
A 10-parameter Bayesian logistic regression model (BLRM) with the overdose control (EWOC) principle guided the dose escalation of the combination treatment to the MTD(s) and/or RDE(s). The BLRM for each combination treatment was

fitted on the cycle 1 Dose limiting toxicity (DLT) data (i.e. absence or presence of DLT) accumulated throughout the dose escalation to model the dose-DLT relationship of each combination treatment. No formal hypothesis was tested.

The Safety Set was used for summaries and listings of safety data with the exception of DLTs for which the dose determining set (DDS) was used.

Analysis of secondary endpoints:
Efficacy:
Full analysis set was used for efficacy analysis.

- Spleen volume: percent change in spleen volume from baseline at post-baseline visits, proportion of patients achieving ≥ 35% reduction in spleen volume from baseline at Week 24 were summarized descriptively by treatment group in each treatment arm. Duration of spleen volume response was estimated by Kaplan-Meier estimates.
- JAK2V617F allele burden: percentage allele burden at baseline and post-baseline and proportion of patients achieving ≥ 50% allele burden reduction at Week 24 were summarized descriptively by treatment group in each treatment arm.
- Bone marrow histomorphology: change in bone marrow histomorphology and shifts from baseline in bone marrow fibrosis grade (from biopsy sample) to worst post-baseline were summarized descriptively by treatment group within each treatment arm.
- Hematological changes: change from baseline in platelets, neutrophils and hemoglobin at each visit and shift in common terminology criteria for adverse events (CTCAE) grades for hematological parameters comparing baseline to the worst on-treatment value were summarized descriptively by treatment group within each treatment arm.

Pharmacokinetics:
All pharmacokinetic data analyses and Pharmacokinetic(s) (PK) summary statistics were based on pharmacokinetic analysis set (PAS). PK parameters for PIM447, ruxolitinib, and LEE011 were determined using noncompartmental methods. Concentrations below the LLOQ (and LEQ803) were treated as zero in summary statistics and were handled as missing for the calculation of the geometric means and their coefficient of variation (CV).

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:
-Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2.
-Patient must be diagnosed with JAK2V617F-positive primary or secondary Myelofibrosis (MF).
-Dose-escalation and Expansion parts: Patients with a < 35% reduction in spleen volume by Magnetic resonance imaging (MRI)/computed tomography (CT) or < 50% reduction in spleen size by physical exam, with or without corresponding symptomatic improvement, after at least 6 months of treatment with single agent ruxolitinib at an optimal dose level in line with the label recommendations. Expansion parts only: Ruxolitinib-naive patients and patients who have been previously treated with single agent ruxolitinib and are relapsed and/or refractory.
-Patients must have splenomegaly measuring at least 5 cm by MRI at baseline.
-Have adequate bone marrow function:
•Platelets ≥ 100,000 mm3 without the assistance of growth factors or platelet transfusions
•Absolute Neutrophil Count (ANC) ≥ 1500/mm3 without growth factor support within 7 days prior to testing
•Hemoglobin ≥ 9 g/dL.

Exclusion Criteria:
-Systemic antineoplastic therapy (including unconjugated therapeutic antibodies, toxin immunoconjugates, and alpha-interferon) or any experimental therapy within 14 days or 5 half-lives, whichever is shorter, before the first dose of study treatment
-Major surgery within 2 weeks before the first dose of either study drug.
-Patients who have had splenic irradiation within 2 weeks prior to Screening or prior splenectomy.
-Patients with Acute myeloid leukemia (AML), Myelodysplastic syndrome (MDS), or peripheral blasts ≥ 10 %
-Prior autologous or allogeneic stem cell transplant at any time.
-Patients who are currently receiving treatment with a prohibited medication that cannot be discontinued at least one week prior to the start of treatment:
•substrates of CYP3A4/5, CYP2B6 or CYP2D6 that have a narrow therapeutic window
•strong inhibitors of CYP3A4/5 or CYP2D6
•potent inducers of CYP3A4/5 or CYP2D6
-Serum total bilirubin > 1.5 x upper limit of normal (ULN) except in patients with Gilbert's syndrome who are excluded if the total bilirubin is > 3.0 x ULN or direct bilirubin > 1.5 x ULN, or aspartate aminotransferase (AST) (serum glutamic oxaloacetic transaminase [SGOT]) or ALT (SGPT) > 3 x ULN, except in patients with MF involvement of the liver who are excluded if AST or ALT > 5 x ULN.
-Serum creatinine > 1.5 x ULN or calculated creatinine clearance < 60 ml/min according to Cockcroft-Gault equation
-Electrolyte abnormalities Common terminology criteria for adverse events (CTCAE) grade ≥ 2 (e.g. serum potassium, magnesium and calcium) unless they can be repleted during screening and are deemed not clinically significant by the Investigator.

Participant Flow Table

Overall Study

	PIM447 150 mg QD + Ruxolitinib 5 mg BID	LEE011 200 mg QD+ Ruxolitinib 5 mg BID	LEE011 200 mg QD+ Ruxolitinib 10 mg BID	PIM447 100 mg QD+ Ruxolitinib 5 mg BID+LEE011 200 mg QD	PIM447 100 mg QD+ Ruxolitinib 10 mg BID+LEE011 200 mg QD	Total
Arm/Group Description	PIM447 150 mg QD + Ruxolitinib 5 mg BID	LEE011 200 mg QD+ Ruxolitinib 5 mg BID	LEE011 200 mg QD+ Ruxolitinib 10 mg BID	PIM447 100 mg QD+ Ruxolitinib 5 mg BID+LEE011 200 mg QD	PIM447 100 mg QD+ Ruxolitinib 10 mg BID+LEE011 200 mg QD	
Started	5	3	2	3	2	15
Completed	0	0	0	0	0	0
Not Completed	5	3	2	3	2	15
Withdrawal by Subject	0	1	0	1	0	2
Physician Decision	0	1	1	0	0	2
Progressive Disease	1	1	1	1	2	6
Death	1	0	0	0	0	1
Adverse Event	3	0	0	1	0	4

Baseline Characteristics

	PIM447 150 mg QD + Ruxolitinib 5 mg BID	LEE011 200 mg QD+ Ruxolitinib 5 mg BID	LEE011 200 mg QD+ Ruxolitinib 10 mg BID	PIM447 100 mg QD+ Ruxolitinib 5 mg BID+LEE011 200 mg QD	PIM447 100 mg QD+ Ruxolitinib 10 mg BID+LEE011 200 mg QD	Total
Arm/Group Description	PIM447 150 mg QD + Ruxolitinib 5 mg BID	LEE011 200 mg QD+ Ruxolitinib 5 mg BID	LEE011 200 mg QD+ Ruxolitinib 10 mg BID	PIM447 100 mg QD+ Ruxolitinib 5 mg BID+LEE011 200 mg QD	PIM447 100 mg QD+ Ruxolitinib 10 mg BID+LEE011 200 mg QD	
Number of Participants [units: participants]	5	3	2	3	2	15
Age Categorical (units: Participants) Count of Participants (Not Applicable)						
<=18 years	0	0	0	0	0	0
Between 18 and 65 years	2	1	2	1	1	7
>=65 years	3	2	0	2	1	8
Age Continuous (units: years) Mean ± Standard Deviation						
	66.2±9.07	66.0±3.00	59.5±0.71	68.3±6.03	60.5±7.78	64.9±6.68
Sex: Female, Male (units: Participants) Count of Participants (Not Applicable)						
Female	0	2	0	0	1	3
Male	5	1	2	3	1	12

Race/Ethnicity, Customized (units: Participants)						
Caucasian	3	1	1	2	2	9
Asian	1	1	1	0	0	3
Other	1	1	0	1	0	3

Primary Outcome Result(s)

Incidence of dose limiting toxicities during the first cycle of study treatment

(Time Frame: Cycle 1 (up to Day 28))

	PIM447 150 mg QD + Ruxolitinib 5 mg BID	**LEE011 200 mg QD+ Ruxolitinib 5 mg BID**	**LEE011 200 mg QD+ Ruxolitinib 10 mg BID**	**PIM447 100 mg QD+ Ruxolitinib 5 mg BID+LEE011 200 mg QD**	**PIM447 100 mg QD+ Ruxolitinib 10 mg BID+LEE011 200 mg QD**
Arm/Group Description	PIM447 150 mg QD + Ruxolitinib 5 mg BID	LEE011 200 mg QD+ Ruxolitinib 5 mg BID	LEE011 200 mg QD+ Ruxolitinib 10 mg BID	PIM447 100 mg QD+ Ruxolitinib 5 mg BID+LEE011 200 mg QD	PIM447 100 mg QD+ Ruxolitinib 10 mg BID+LEE011 200 mg QD
Number of Participants Analyzed [units: participants]	5	3	2	3	2
Incidence of dose limiting toxicities during the first cycle of study treatment (units: Participants) Count of Participants (Not Applicable)					
Dyspepsia - all grades	1 (20%)	0 (%)	0 (%)	0 (%)	0 (%)
Lymphopenia - all grades	0 (%)	0 (%)	0 (%)	0 (%)	1 (50%)

Neutropenia - all grades	0 (%)	0 (%)	0 (%)	0 (%)	1 (50%)
Thrombocytopenia - all grades	0 (%)	0 (%)	0 (%)	0 (%)	1 (50%)

Secondary Outcome Result(s)

Number and percentage of patients achieving ≥ 35% reduction in spleen volume by magnetic resonance imaging (MRI) at Week 24

(Time Frame: Baseline and Week 24)

	PIM447 150 mg QD + Ruxolitinib 5 mg BID	LEE011 200 mg QD+ Ruxolitinib 5 mg BID	LEE011 200 mg QD+ Ruxolitinib 10 mg BID	PIM447 100 mg QD+ Ruxolitinib 5 mg BID+LEE011 200 mg QD	PIM447 100 mg QD+ Ruxolitinib 10 mg BID+LEE011 200 mg QD
Arm/Group Description	PIM447 150 mg QD + Ruxolitinib 5 mg BID	LEE011 200 mg QD+ Ruxolitinib 5 mg BID	LEE011 200 mg QD+ Ruxolitinib 10 mg BID	PIM447 100 mg QD+ Ruxolitinib 5 mg BID+LEE011 200 mg QD	PIM447 100 mg QD+ Ruxolitinib 10 mg BID+LEE011 200 mg QD
Number of Participants Analyzed [units: participants]	5	3	2	3	2
Number and percentage of patients achieving ≥ 35% reduction in spleen volume by magnetic resonance imaging (MRI) at Week 24 (units: Participants) Count of Participants (Not Applicable)					
Number of patients with a valid baseline spleen assessment	5 (100%)	3 (100%)	2 (100%)	3 (100%)	2 (100%)

Number of patients with a valid spleen assessment at Week 24	2 (40%)	2 (66.67%)	2 (100%)	2 (66.67%)	2 (100%)
Number of patients achieving at least 35% reduction in spleen volume at week 24	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)
Number of patients with a valid spleen assessment at any time postbaseline	3 (60%)	3 (100%)	2 (100%)	2 (66.67%)	2 (100%)
Number of patients achieving at least 35% reduction in spleen volume	1 (20%)	1 (33.33%)	1 (50%)	0 (%)	0 (%)

Change from baseline in patients achieving at least 35% reduction in spleen volume

(Time Frame: Study Days 85, 169, 253, 337, 505, 673, 841, 1009, 1177, 1345, 1513, 1681, 1849, and EOT (max Day 1903))

	PIM447 150 mg QD + Ruxolitinib 5 mg BID	LEE011 200 mg QD+ Ruxolitinib 5 mg BID	LEE011 200 mg QD+ Ruxolitinib 10 mg BID	PIM447 100 mg QD+ Ruxolitinib 5 mg BID+LEE011 200 mg QD	PIM447 100 mg QD+ Ruxolitinib 10 mg BID+LEE011 200 mg QD
Arm/Group Description	PIM447 150 mg QD + Ruxolitinib 5 mg BID	LEE011 200 mg QD+ Ruxolitinib 5 mg BID	LEE011 200 mg QD+ Ruxolitinib 10 mg BID	PIM447 100 mg QD+ Ruxolitinib 5 mg BID+LEE011 200 mg QD	PIM447 100 mg QD+ Ruxolitinib 10 mg BID+LEE011 200 mg QD
Number of Participants Analyzed [units: participants]	3	3	2	2	2
Change from baseline in patients achieving at least 35% reduction in spleen volume (units: mm3) Mean ± Standard Deviation					
Change from Baseline - Cycle 4 Day 1 (Day 85)	-479421 ± 785802.343	269608.33 ± 879450.285	233751 ± 1470841.502	-1073791 ± 161883.612	-1211633.5 ± 2082345.325

Change from Baseline - Cycle 7 Day 1 (Day 169)(n=2,2,2,2,2)	-1144208 ± 1862707.352	-341173 ± 588147.379	115047 ± 1618706.015	-1337396 ± 373950.593	-773050.5 ± 1823061.996
Change from Baseline - Cycle 10 Day 1 (Day 253) (n=2,2,2,1,1)	-1010778 ± 2475971.164	-266776.5 ± 487953.884	-205505.5 ± 1392639.027	-779809 ± NA[12345678910111213141516171 8192021]	645227 ± NA[12345678910111213141516171 8192021]
Change from Baseline - Cycle 13 Day 1 (Day 337)(n=2,2,1,1,1)	-1627997 ± 3817526.676	-183417 ± 291046.565	-1261221 ± NA[12345678910111213141516171 8192021]	-752833 ± NA[12345678910111213141516171 8192021]	493856 ± NA[12345678910111213141516171 8192021]
Change from Baseline - Cycle 19 Day 1 (Day 505)(n=1,2,1,0,1)	-3650012 ± NA[12345678910111213141516171 8192021]	-229303.5 ± 370784.876	-1458883 ± NA[12345678910111213141516171 8192021]		886912 ± NA[12345678910111213141516171 8192021]
Change from Baseline - Cycle 25 Day 1 (Day 673)(n=0,2,1,0,1)		-367173.5 ± 582047.169	-1553791 ± NA[12345678910111213141516171 8192021]		1417222 ± NA[12345678910111213141516171 8192021]
Change from Baseline - Cycle 31 Day 1 (Day 841)(n=1,1,1,0,0)	-3768833 ± NA[12345678910111213141516171 8192021]	-721708 ± NA[12345678910111213141516171 8192021]	-1563183 ± NA[12345678910111213141516171 8192021]		

Change from Baseline - Cycle 37 Day 1 (Day 1009)(n=0,2,1, 0,0)	-359876 ± 653536.371	-1226318 ± NA[12345678910111213141516171 8192021]
Change from Baseline - Cycle 43 Day 1 (Day 1177)(N=0,2,1, 0,0)	-315671 ± 703130.013	-418196 ± NA[12345678910111213141516171 8192021]
Change from Baseline - Cycle 49 Day 1 (Day 1345)(n=0,1,0, 0,0)	-892451 ± NA[12345678910111213141516171 8192021]	
Change from Baseline - Cycle 55 Day 1 (Day 1513)(n=0,2,0, 0,0)	-294923 ± 896559.073	
Change from Baseline - Cycle 61 Day 1 (Day 1681)(N=0,1,0, 0,0)	-1171781 ± NA[12345678910111213141516171 8192021]	
Change from Baseline - Cycle 67 Day 1 (Day 1849)(N=0,1,0, 0,0)	-779408 ± NA[12345678910111213141516171 8192021]	

Change from Baseline - EOT (Max Day 1903)(n=1,1,0, 1,0)	-1392233 ± NA[12345678910111213141516171 8192021]	373967 ± NA[12345678910111213141516171 8192021]	-2641827 ± NA[12345678910111213141516171 8192021]

[1] SD is NA if the analysis set = 1.
[2] SD is NA if the analysis set = 1.
[3] SD is NA if the analysis set = 1.
[4] SD is NA if the analysis set = 1.
[5] SD is NA if the analysis set = 1.
[6] SD is NA if the analysis set = 1.
[7] SD is NA if the analysis set = 1.
[8] SD is NA if the analysis set = 1.
[9] SD is NA if the analysis set = 1.
[10] SD is NA if the analysis set = 1.
[11] SD is NA if the analysis set = 1.
[12] SD is NA if the analysis set = 1.
[13] SD is NA if the analysis set = 1.
[14] SD is NA if the analysis set = 1.
[15] SD is NA if the analysis set = 1.
[16] SD is NA if the analysis set = 1.
[17] SD is NA if the analysis set = 1.
[18] SD is NA if the analysis set = 1.
[19] SD is NA if the analysis set = 1.
[20] SD is NA if the analysis set = 1.
[21] SD is NA if the analysis set = 1.

Changes in JAK2V617F allele burden

(Time Frame: Baseline, Week 12, Week 24, Week 48, Week 72, Week 96)

	PIM447 150 mg QD + Ruxolitinib 5 mg BID	LEE011 200 mg QD+ Ruxolitinib 5 mg BID	LEE011 200 mg QD+ Ruxolitinib 10 mg BID	PIM447 100 mg QD+ Ruxolitinib 5 mg BID+LEE011 200 mg QD	PIM447 100 mg QD+ Ruxolitinib 10 mg BID+LEE011 200 mg QD
Arm/Group Description	PIM447 150 mg QD + Ruxolitinib 5 mg BID	LEE011 200 mg QD+ Ruxolitinib 5 mg BID	LEE011 200 mg QD+ Ruxolitinib 10 mg BID	PIM447 100 mg QD+ Ruxolitinib 5 mg BID+LEE011 200 mg QD	PIM447 100 mg QD+ Ruxolitinib 10 mg BID+LEE011 200 mg QD

Number of Participants Analyzed [units: participants]	2	2	1	2	2
Changes in JAK2V617F allele burden (units: Number) Median (Full Range)					
Baseline (n=0,0,0,1,2)				51.275 (51.275 to 51.275)	90.198 (86.508 to 93.887)
Week 12 (n=0,0,1,2,2)			85.526 (85.526 to 85.526)	69.505 (49.310 to 89.699)	82.078 (74.700 to 89.457)
Week 24 (n=0,0,0,2,2)				67.963 (50.143 to 85.783)	87.434 (84.520 to 90.347)
Week 48 (n=1,0,1,1,1)	79.933 (79.933 to 79.933)		83.392 (83.392 to 83.392)	89.494 (89.494 to 89.494)	84.106 (84.106 to 84.106)
Week 72 (n=2,2,1,0,1)	71.317 (55.187 to 87.448)	62.266 (41.818 to 82.714)	79.636 (79.636 to 79.636)		85.259 (85.259 to 85.259)
Week 96 (n=1,2,0,0,1)	86.869 (86.869 to 86.869)	60.592 (42.680 to 78.504)			90.010 (90.010 to 90.010)

Change in bone marrow histomorphology

(Time Frame: Baseline, Cycle 7 at Day 1 (Day 169), and End of Trial (EOT) (maximum approx 5.21 years))

PIM447 150 mg QD + Ruxolitinib 5 mg BID	LEE011 - All Patients (LEE 200 mg q.d.+ RUX 5 mg b.i.d. and LEE 200 mg q.d.+ RUX 10 mg b.i.d)	PIM447-All Pts(PIM100mg QD+RUX5mg BID+LEE200mg QD and PIM100mg QD+RUX10 mg

			BID+LEE200mg QD)
Arm/Group Description	PIM447 150 mg QD + Ruxolitinib 5 mg BID	All Patients (LEE 200 mg q.d.+RUX 5 mg b.i.d.and LEE 200 mg q.d.+ RUX 10 mg b.i.d)	PIM447 - All Patients (PIM 100 mg QD+ RUX 5 mg BID + LEE 200 mg QD and PIM 100 mg QD+ RUX 10 mg BID + LEE 200 mg QD)
Number of Participants Analyzed [units: participants]	1	2	2
Change in bone marrow histomorphology (units: Percentage) Median (Full Range)			
% Blast cells (Biopsy) - change from baseline at Cycle 7 Day 1 (n=1,1,2)	0 (0 to 0)	0 (0 to 0)	-1 (-1 to -1)
% Cellularity (Biopsy) - change from baseline at Cycle 7 Day 1 (n=1,2,2)	0 (0 to 0)	-10 (-20 to 0)	-12.5 (-25 to 0)
% Blast cells (Aspirate) - change from baseline at Cycle 7 Day 1 (n=0,1,0)		-4 (-4 to -4)	
% Blast cells (Biopsy) - change from baseline at EOT (maximum approx 5.21 years) (n=0,1,0)		-6 (-6 to -6)	
% Cellularity (Biopsy) - change from baseline at EOT (maximum approx 5.21 years) (n=0,0,0)			
% Blast cells (Aspirate) - change from baseline at		-6 (-6 to -6)	

EOT (maximum approx 5.21 years) (n=0,1,0)

Change in bone marrow fibrosis - Worst post-baseline value

(Time Frame: Baseline, Cycle 7 at Day 1 (Day 169), and End of Trial (EOT) (maximum approx 5.21 years))

	PIM447 150 mg QD + Ruxolitinib 5 mg BID	LEE011 200 mg QD+ Ruxolitinib 5 mg BID	LEE011 200 mg QD+ Ruxolitinib 10 mg BID	PIM447 100 mg QD+ Ruxolitinib 5 mg BID+LEE011 200 mg QD	PIM447 100 mg QD+ Ruxolitinib 10 mg BID+LEE011 200 mg QD
Arm/Group Description	PIM447 150 mg QD + Ruxolitinib 5 mg BID	LEE011 200 mg QD+ Ruxolitinib 5 mg BID	LEE011 200 mg QD+ Ruxolitinib 10 mg BID	PIM447 100 mg QD+ Ruxolitinib 5 mg BID+LEE011 200 mg QD	PIM447 100 mg QD+ Ruxolitinib 10 mg BID+LEE011 200 mg QD
Number of Participants Analyzed [units: participants]	5	3	2	3	2
Change in bone marrow fibrosis - Worst post-baseline value (units: Participants) Count of Participants (Not Applicable)					
Grade 0	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)
Grade 1	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)
Grade 2	0 (%)	1 (33.33%)	1 (50%)	1 (33.33%)	0 (%)
Grade 3	2 (40%)	1 (33.33%)	1 (50%)	1 (33.33%)	1 (50%)
Grade 4	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)
Missing	3 (60%)	1 (33.33%)	0 (%)	1 (33.33%)	1 (50%)

Plasma pharmacokinetics (PK) for PIM447 - AUClast

(Time Frame: Cycle 1 Day 1 and Cycle 1 Day 15)

	PIM447 150 mg QD + Ruxolitinib 5 mg BID	PIM447 100 mg QD+ Ruxolitinib 5 mg BID+LEE011 200 mg QD	PIM447 100 mg QD+ Ruxolitinib 10 mg BID+LEE011 200 mg QD
Arm/Group Description	PIM447 150 mg QD + Ruxolitinib 5 mg BID	PIM447 100 mg QD+ Ruxolitinib 5 mg BID+LEE011 200 mg QD	PIM447 100 mg QD+ Ruxolitinib 10 mg BID+LEE011 200 mg QD
Number of Participants Analyzed [units: participants]	5	3	2
Plasma pharmacokinetics (PK) for PIM447 - AUClast (units: hr*ng/mL) Geometric Mean (Geometric Coefficient of Variation)			
Cycle 1 Day 1	18100 (33.2%)	11300 (156%)	17100 (83.4%)
Cycle 1 Day 15 (n=3,3,2)	43000 (20.0%)	34700 (87.6%)	34100 (136%)

Plasma pharmacokinetics (PK) for PIM447 - Cmax

(Time Frame: Cycle 1 Day 1 and Cycle 1 Day 15)

	PIM447 150 mg QD + Ruxolitinib 5 mg BID	PIM447 100 mg QD+ Ruxolitinib 5 mg BID+LEE011 200 mg QD	PIM447 100 mg QD+ Ruxolitinib 10 mg BID+LEE011 200 mg QD
Arm/Group Description	PIM447 150 mg QD +	PIM447 100 mg QD+ Ruxolitinib 5	PIM447 100 mg QD+ Ruxolitinib 10

	Ruxolitinib 5 mg BID	mg BID+LEE011 200 mg QD	mg BID+LEE011 200 mg QD
Number of Participants Analyzed [units: participants]	5	3	2
Plasma pharmacokinetics (PK) for PIM447 - Cmax (units: ng/mL) Geometric Mean (Geometric Coefficient of Variation)			
Cycle 1 Day 1	1140 (33.3%)	936 (118%)	1280 (77.4%)
Cycle 1 Day 15 (n=3,3,2)	2400 (7.92%)	2210 (74.6%)	1860 (137%)

Plasma pharmacokinetics (PK) for PIM447 - Racc

(Time Frame: Cycle 1 Day 1 and Cycle 1 Day 15)

	PIM447 150 mg QD + Ruxolitinib 5 mg BID	**PIM447 100 mg QD+ Ruxolitinib 5 mg BID+LEE011 200 mg QD**	**PIM447 100 mg QD+ Ruxolitinib 10 mg BID+LEE011 200 mg QD**
Arm/Group Description	PIM447 150 mg QD + Ruxolitinib 5 mg BID	PIM447 100 mg QD+ Ruxolitinib 5 mg BID+LEE011 200 mg QD	PIM447 100 mg QD+ Ruxolitinib 10 mg BID+LEE011 200 mg QD
Number of Participants Analyzed [units: participants]	3	3	2
Plasma pharmacokinetics (PK) for PIM447 - Racc (units: hr*ng/mL/hr*ng/mL) Geometric Mean			

(Geometric Coefficient of Variation)			
Cycle 1 Day 15	2.62 (47.7%)	3.07 (41.3%)	1.99 (30.3%)

Plasma pharmacokinetics (PK) for PIM447 - T1/2

(Time Frame: Cycle 1 Day 1 and Cycle 1 Day 15)

	PIM447 150 mg QD + Ruxolitinib 5 mg BID	**PIM447 100 mg QD+ Ruxolitinib 5 mg BID+LEE011 200 mg QD**	**PIM447 100 mg QD+ Ruxolitinib 10 mg BID+LEE011 200 mg QD**
Arm/Group Description	PIM447 150 mg QD + Ruxolitinib 5 mg BID	PIM447 100 mg QD+ Ruxolitinib 5 mg BID+LEE011 200 mg QD	PIM447 100 mg QD+ Ruxolitinib 10 mg BID+LEE011 200 mg QD
Number of Participants Analyzed [units: participants]	1	1	2
Plasma pharmacokinetics (PK) for PIM447 - T1/2 (units: hr) Median (Full Range)			
Cycle 1 Day 1	22.5 (22.5 to 22.5)	21.5 (21.5 to 21.5)	17.3 (15.7 to 18.9)
Cycle 1 Day 15 (n=1,1,0)	20.3 (20.3 to 20.3)	21.9 (21.9 to 21.9)	

Plasma pharmacokinetics (PK) for PIM447 - Tmax

(Time Frame: Cycle 1 Day 1 and Cycle 1 Day 15)

	PIM447 150 mg QD +	**PIM447 100 mg QD+ Ruxolitinib 5**	**PIM447 100 mg QD+ Ruxolitinib**

	Ruxolitinib 5 mg BID	mg BID+LEE011 200 mg QD	10 mg BID+LEE011 200 mg QD
Arm/Group Description	PIM447 150 mg QD + Ruxolitinib 5 mg BID	PIM447 100 mg QD+ Ruxolitinib 5 mg BID+LEE011 200 mg QD	PIM447 100 mg QD+ Ruxolitinib 10 mg BID+LEE011 200 mg QD
Number of Participants Analyzed [units: participants]	5	3	2
Plasma pharmacokinetics (PK) for PIM447 - Tmax (units: hr) Median (Full Range)			
Cycle 1 Day 1	2.07 (0.950 to 4.00)	3.85 (1.00 to 23.1)	2.00 (2.00 to 2.00)
Cycle 1 Day 15 (n=3,3,2)	3.92 (2.17 to 4.17)	2.00 (2.00 to 4.00)	3.00 (2.00 to 4.00)

Plasma pharmacokinetics (PK) for ruxolitinib - AUClast

(Time Frame: Cycle 1 Day 1 and Cycle 1 Day 15)

	PIM447 150 mg QD + Ruxolitinib 5 mg BID	LEE011 200 mg QD+ Ruxolitinib 5 mg BID	LEE011 200 mg QD+ Ruxolitinib 10 mg BID	PIM447 100 mg QD+ Ruxolitinib 5 mg BID+LEE011 200 mg QD	PIM447 100 mg QD+ Ruxolitinib 10 mg BID+LEE011 200 mg QD
Arm/Group Description	PIM447 150 mg QD + Ruxolitinib 5 mg BID	LEE011 200 mg QD+ Ruxolitinib 5 mg BID	LEE011 200 mg QD+ Ruxolitinib 10 mg BID	PIM447 100 mg QD+ Ruxolitinib 5 mg BID+LEE011 200 mg QD	PIM447 100 mg QD+ Ruxolitinib 10 mg BID+LEE011 200 mg QD

Number of Participants Analyzed [units: participants]	5	3	2	3	2
Plasma pharmacokinetics (PK) for ruxolitinib - AUClast (units: hr*ng/mL) Geometric Mean (Geometric Coefficient of Variation)					
Cycle 1 Day 1	161 (88.5%)	199 (34.6%)	301 (33.9%)	150 (28.9%)	250 (302%)
Cycle 1 Day 15 (n=4,3,2,3,2)	105 (55.8%)	205 (62.3%)	348 (9.82%)	158 (32.3%)	648 (51.9%)

Plasma pharmacokinetics (PK) for ruxolitinib - Cmax

(Time Frame: Cycle 1 Day 1 and Cycle 1 Day 15)

	PIM447 150 mg QD + Ruxolitinib 5 mg BID	**LEE011 200 mg QD+ Ruxolitinib 5 mg BID**	**LEE011 200 mg QD+ Ruxolitinib 10 mg BID**	**PIM447 100 mg QD+ Ruxolitinib 5 mg BID+LEE011 200 mg QD**	**PIM447 100 mg QD+ Ruxolitinib 10 mg BID+LEE011 200 mg QD**
Arm/Group Description	PIM447 150 mg QD + Ruxolitinib 5 mg BID	LEE011 200 mg QD+ Ruxolitinib 5 mg BID	LEE011 200 mg QD+ Ruxolitinib 10 mg BID	PIM447 100 mg QD+ Ruxolitinib 5 mg BID+LEE011 200 mg QD	PIM447 100 mg QD+ Ruxolitinib 10 mg BID+LEE011 200 mg QD
Number of Participants Analyzed [units: participants]	5	3	2	3	2
Plasma pharmacokinetics (PK) for ruxolitinib - Cmax (units: ng/mL) Geometric Mean (Geometric Coefficient of Variation)					
Cycle 1 Day 1	63.9 (61.2%)	76.9 (20.8%)	99.6 (107%)	67.7 (23.3%)	85.8 (333%)
Cycle 1 Day 15 (n=4,3,2,3,2)	35.6 (63.8%)	78.6 (47.2%)	93.4 (12.4%)	58.3 (30.6%)	189 (93.1%)

Plasma pharmacokinetics (PK) for ruxolitinib - Racc

(Time Frame: Cycle 1 Day 1 and Cycle 1 Day 15)

	PIM447 150 mg QD + Ruxolitinib 5 mg BID	LEE011 200 mg QD+ Ruxolitinib 5 mg BID	LEE011 200 mg QD+ Ruxolitinib 10 mg BID	PIM447 100 mg QD+ Ruxolitinib 5 mg BID+LEE011 200 mg QD	PIM447 100 mg QD+ Ruxolitinib 10 mg BID+LEE011 200 mg QD
Arm/Group Description	PIM447 150 mg QD + Ruxolitinib 5 mg BID	LEE011 200 mg QD+ Ruxolitinib 5 mg BID	LEE011 200 mg QD+ Ruxolitinib 10 mg BID	PIM447 100 mg QD+ Ruxolitinib 5 mg BID+LEE011 200 mg QD	PIM447 100 mg QD+ Ruxolitinib 10 mg BID+LEE011 200 mg QD
Number of Participants Analyzed [units: participants]	4	3	2	3	2
Plasma pharmacokinetics (PK) for ruxolitinib - Racc (units: hr*ng/mL/hr*ng/mL) Geometric Mean (Geometric Coefficient of Variation)					
Cycle 1 Day 15	0.795 (56.4%)	1.03 (26.0%)	1.15 (44.8%)	1.06 (3.85%)	2.60 (138%)

Plasma pharmacokinetics (PK) for ruxolitinib - T1/2

(Time Frame: Cycle 1 Day 1 and Cycle 1 Day 15)

	PIM447 150 mg QD + Ruxolitinib 5 mg BID	LEE011 200 mg QD+ Ruxolitinib 5 mg BID	LEE011 200 mg QD+ Ruxolitinib 10 mg BID	PIM447 100 mg QD+ Ruxolitinib 5 mg BID+LEE011 200 mg QD	PIM447 100 mg QD+ Ruxolitinib 10 mg BID+LEE011 200 mg QD
Arm/Group Description	PIM447 150 mg QD +	LEE011 200 mg QD+	LEE011 200 mg QD+	PIM447 100 mg QD+	PIM447 100 mg QD+

	Ruxolitinib 5 mg BID	Ruxolitinib 5 mg BID	Ruxolitinib 10 mg BID	Ruxolitinib 5 mg BID+LEE011 200 mg QD	Ruxolitinib 10 mg BID+LEE011 200 mg QD
Number of Participants Analyzed [units: participants]	5	3	2	3	2
Plasma pharmacokinetics (PK) for ruxolitinib - T1/2 (units: hr) Median (Full Range)					
Cycle 1 Day 1	2.08 (0.814 to 3.07)	1.73 (1.38 to 3.05)	2.44 (1.32 to 3.56)	1.68 (1.46 to 1.97)	2.73 (2.53 to 2.93)
Cycle 1 Day 15 (n=3,3,1,3,2)	1.93 (0.837 to 2.59)	1.91 (1.18 to 2.69)	3.48 (3.48 to 3.48)	1.71 (1.57 to 1.74)	3.55 (3.17 to 3.92)

Plasma pharmacokinetics (PK) for ruxolitinib - Tmax

(Time Frame: Cycle 1 Day 1 and Cycle 1 Day 15)

	PIM447 150 mg QD + Ruxolitinib 5 mg BID	**LEE011 200 mg QD+ Ruxolitinib 5 mg BID**	**LEE011 200 mg QD+ Ruxolitinib 10 mg BID**	**PIM447 100 mg QD+ Ruxolitinib 5 mg BID+LEE011 200 mg QD**	**PIM447 100 mg QD+ Ruxolitinib 10 mg BID+LEE011 200 mg QD**
Arm/Group Description	PIM447 150 mg QD + Ruxolitinib 5 mg BID	LEE011 200 mg QD+ Ruxolitinib 5 mg BID	LEE011 200 mg QD+ Ruxolitinib 10 mg BID	PIM447 100 mg QD+ Ruxolitinib 5 mg BID+LEE011 200 mg QD	PIM447 100 mg QD+ Ruxolitinib 10 mg BID+LEE011 200 mg QD
Number of Participants Analyzed [units: participants]	5	3	2	3	2

Plasma pharmacokinetics (PK) for ruxolitinib - Tmax (units: hr) Median (Full Range)					
Cycle 1 Day 1	0.500 (0.467 to 0.667)	1.00 (0.650 to 1.00)	0.750 (0.500 to 1.00)	0.500 (0.433 to 0.800)	0.250 (0.00 to 0.500)
Cycle 1 Day 15 (n=4,3,2,3,2)	0.792 (0.583 to 4.25)	0.583 (0.500 to 1.00)	1.50 (1.00 to 2.00)	1.00 (0.583 to 1.05)	0.500 (0.500 to 0.500)

Plasma pharmacokinetics (PK) for ruxolitinib - AUCinf

(Time Frame: Cycle 1 Day 1 and Cycle 1 Day 15)

	PIM447 150 mg QD + Ruxolitinib 5 mg BID	**LEE011 200 mg QD+ Ruxolitinib 5 mg BID**	**LEE011 200 mg QD+ Ruxolitinib 10 mg BID**	**PIM447 100 mg QD+ Ruxolitinib 5 mg BID+LEE011 200 mg QD**	**PIM447 100 mg QD+ Ruxolitinib 10 mg BID+LEE011 200 mg QD**
Arm/Group Description	PIM447 150 mg QD + Ruxolitinib 5 mg BID	LEE011 200 mg QD+ Ruxolitinib 5 mg BID	LEE011 200 mg QD+ Ruxolitinib 10 mg BID	PIM447 100 mg QD+ Ruxolitinib 5 mg BID+LEE011 200 mg QD	PIM447 100 mg QD+ Ruxolitinib 10 mg BID+LEE011 200 mg QD
Number of Participants Analyzed [units: participants]	5	3	1	3	2
Plasma pharmacokinetics (PK) for ruxolitinib - AUCinf (units: hr*ng/mL) Geometric Mean (Geometric Coefficient of Variation)					
Cycle 1 Day 1(n=5,3,1,3,2)	175 (97.8%)	223 (42.7%)	388 (NA%)[12]	157 (28.9%)	293 (299%)
Cycle 1 Day 15 (n=3,3,0,3,1)	127 (69.1%)	223 (68.4%)		165 (32.3%)	1130 (NA%)[12]

[1] Geometric Coefficient of Variation is NA for n analyzed =1
[2] Geometric Coefficient of Variation is NA for n analyzed =1

Plasma pharmacokinetics (PK) for ruxolitinib - CL/F

(Time Frame: Cycle 1 Day 1 and Cycle 1 Day 15)

	PIM447 150 mg QD + Ruxolitinib 5 mg BID	LEE011 200 mg QD+ Ruxolitinib 5 mg BID	LEE011 200 mg QD+ Ruxolitinib 10 mg BID	PIM447 100 mg QD+ Ruxolitinib 5 mg BID+LEE011 200 mg QD	PIM447 100 mg QD+ Ruxolitinib 10 mg BID+LEE011 200 mg QD
Arm/Group Description	PIM447 150 mg QD + Ruxolitinib 5 mg BID	LEE011 200 mg QD+ Ruxolitinib 5 mg BID	LEE011 200 mg QD+ Ruxolitinib 10 mg BID	PIM447 100 mg QD+ Ruxolitinib 5 mg BID+LEE011 200 mg QD	PIM447 100 mg QD+ Ruxolitinib 10 mg BID+LEE011 200 mg QD
Number of Participants Analyzed [units: participants]	5	3	1	3	2
Plasma pharmacokinetics (PK) for ruxolitinib - CL/F (units: L/hr) Geometric Mean (Geometric Coefficient of Variation)					
Cycle 1 Day 1(n=5,3,1,3,2)	28.6 (97.8%)	22.5 (42.7%)	25.8 (NA%)[12]	40.1 (66.2%)	48.3 (137%)
Cycle 1 Day 15 (n=3,3,0,3,1)	39.4 (69.1%)	22.4 (68.4%)		38.1 (69.2%)	17.8 (NA%)[12]

[1] Geometric Coefficient of Variation is NA for n analyzed =1
[2] Geometric Coefficient of Variation is NA for n analyzed =1

Plasma pharmacokinetics (PK) for ruxolitinib - Vz/F

(Time Frame: Cycle 1 Day 1 and Cycle 1 Day 15)

	PIM447 150 mg QD + Ruxolitinib 5 mg BID	LEE011 200 mg QD+ Ruxolitinib 5 mg BID	LEE011 200 mg QD+ Ruxolitinib 10 mg BID	PIM447 100 mg QD+ Ruxolitinib 5 mg	PIM447 100 mg QD+ Ruxolitinib 10 mg

				BID+LEE011 200 mg QD	BID+LEE011 200 mg QD
Arm/Group Description	PIM447 150 mg QD + Ruxolitinib 5 mg BID	LEE011 200 mg QD+ Ruxolitinib 5 mg BID	LEE011 200 mg QD+ Ruxolitinib 10 mg BID	PIM447 100 mg QD+ Ruxolitinib 5 mg BID+LEE011 200 mg QD	PIM447 100 mg QD+ Ruxolitinib 10 mg BID+LEE011 200 mg QD
Number of Participants Analyzed [units: participants]	5	3	1	3	2
Plasma pharmacokinetics (PK) for ruxolitinib - Vz/F (units: L) Geometric Mean (Geometric Coefficient of Variation)					
Cycle 1 Day 1(n=5,3,1,3,2)	77.0 (48.6%)	62.8 (7.35%)	49.2 (NA%)[12]	97.9 (80.2%)	190 (161%)
Cycle 1 Day 15 (n=3,3,0,3,1)	91.6 (19.4%)	58.9 (22.5%)		92.0 (71.3%)	81.2 (NA%)[12]

[1] Geometric Coefficient of Variation is NA for n analyzed =1
[2] Geometric Coefficient of Variation is NA for n analyzed =1

Plasma pharmacokinetics (PK) for LEE011 - AUClast

(Time Frame: Cycle 1 Day 1 and Cycle 1 Day 15)

	LEE011 200 mg QD+ Ruxolitinib 5 mg BID	LEE011 200 mg QD+ Ruxolitinib 10 mg BID	PIM447 100 mg QD+ Ruxolitinib 5 mg BID+LEE011 200 mg QD	PIM447 100 mg QD+ Ruxolitinib 10 mg BID+LEE011 200 mg QD
Arm/Group Description	LEE011 200 mg QD+ Ruxolitinib 5 mg BID	LEE011 200 mg QD+ Ruxolitinib 10 mg BID	PIM447 100 mg QD+ Ruxolitinib 5 mg BID+LEE011 200 mg QD	PIM447 100 mg QD+ Ruxolitinib 10 mg BID+LEE011 200 mg QD

Number of Participants Analyzed [units: participants]	3	2	3	2
Plasma pharmacokinetics (PK) for LEE011 - AUClast (units: hr*ng/mL) Geometric Mean (Geometric Coefficient of Variation)				
Cycle 1 Day 1 (n=3,2,3,1)	1480 (46.3%)	1170 (49.1%)	2390 (149%)	4350
Cycle 1 Day 15 (n=3,2,3,2)	3450 (19.8%)	2320 (54.6%)	3620 (62.8%)	4230 (83.1%)

Plasma pharmacokinetics (PK) for LEE011 - Cmax

(Time Frame: Cycle 1 Day 1 and Cycle 1 Day 15)

	LEE011 200 mg QD+ Ruxolitinib 5 mg BID	**LEE011 200 mg QD+ Ruxolitinib 10 mg BID**	**PIM447 100 mg QD+ Ruxolitinib 5 mg BID+LEE011 200 mg QD**	**PIM447 100 mg QD+ Ruxolitinib 10 mg BID+LEE011 200 mg QD**
Arm/Group Description	LEE011 200 mg QD+ Ruxolitinib 5 mg BID	LEE011 200 mg QD+ Ruxolitinib 10 mg BID	PIM447 100 mg QD+ Ruxolitinib 5 mg BID+LEE011 200 mg QD	PIM447 100 mg QD+ Ruxolitinib 10 mg BID+LEE011 200 mg QD
Number of Participants Analyzed [units: participants]	3	2	3	2
Plasma pharmacokinetics (PK) for LEE011 - Cmax (units: ng/mL) Geometric Mean (Geometric Coefficient of Variation)				
Cycle 1 Day 1 (n=3,2,3,1)	223 (66.9%)	108 (97.9%)	280 (68.0%)	467
Cycle 1 Day 15 (n=3,2,3,2)	369 (25.9%)	147 (14.5%)	378 (31.4%)	278 (100%)

Plasma pharmacokinetics (PK) for LEE011 - Racc

(Time Frame: Cycle 1 Day 1 and Cycle 1 Day 15)

	LEE011 200 mg QD+ Ruxolitinib 5 mg BID	LEE011 200 mg QD+ Ruxolitinib 10 mg BID	PIM447 100 mg QD+ Ruxolitinib 5 mg BID+LEE011 200 mg QD	PIM447 100 mg QD+ Ruxolitinib 10 mg BID+LEE011 200 mg QD
Arm/Group Description	LEE011 200 mg QD+ Ruxolitinib 5 mg BID	LEE011 200 mg QD+ Ruxolitinib 10 mg BID	PIM447 100 mg QD+ Ruxolitinib 5 mg BID+LEE011 200 mg QD	PIM447 100 mg QD+ Ruxolitinib 10 mg BID+LEE011 200 mg QD
Number of Participants Analyzed [units: participants]	3	2	3	1
Plasma pharmacokinetics (PK) for LEE011 - Racc (units: hr*ng/mL/hr*ng/mL) Geometric Mean (Geometric Coefficient of Variation)				
Cycle 1 Day 15	2.33 (54.5%)	1.98 (126%)	1.52 (57.4%)	1.62

Plasma pharmacokinetics (PK) for LEE011 - T1/2

(Time Frame: Cycle 1 Day 1 and Cycle 1 Day 15)

	LEE011 200 mg QD+ Ruxolitinib 5 mg BID	LEE011 200 mg QD+ Ruxolitinib 10 mg BID	PIM447 100 mg QD+ Ruxolitinib 5 mg BID+LEE011 200 mg QD	PIM447 100 mg QD+ Ruxolitinib 10 mg BID+LEE011 200 mg QD
Arm/Group Description	LEE011 200 mg QD+	LEE011 200 mg QD+	PIM447 100 mg QD+	PIM447 100 mg QD+

	Ruxolitinib 5 mg BID	Ruxolitinib 10 mg BID	Ruxolitinib 5 mg BID+LEE011 200 mg QD	Ruxolitinib 10 mg BID+LEE011 200 mg QD
Number of Participants Analyzed [units: participants]	3	1	3	2
Plasma pharmacokinetics (PK) for LEE011 - T1/2 (units: hr) Median (Full Range)				
Cycle 1 Day 1 (n=2,1,2,1)	11.7 (8.18 to 15.3)	8.29 (8.29 to 8.29)	11.7 (8.88 to 14.5)	8.43 (8.43 to 8.43)
Cycle 1 Day 15 (n=3,0,3,2)	11.6 (10.4 to 22.4)		13.3 (11.8 to 13.4)	14.4 (13.4 to 15.3)

Plasma pharmacokinetics (PK) for LEE011 - Tmax

(Time Frame: Cycle 1 Day 1 and Cycle 1 Day 15)

	LEE011 200 mg QD+ Ruxolitinib 5 mg BID	**LEE011 200 mg QD+ Ruxolitinib 10 mg BID**	**PIM447 100 mg QD+ Ruxolitinib 5 mg BID+LEE011 200 mg QD**	**PIM447 100 mg QD+ Ruxolitinib 10 mg BID+LEE011 200 mg QD**
Arm/Group Description	LEE011 200 mg QD+ Ruxolitinib 5 mg BID	LEE011 200 mg QD+ Ruxolitinib 10 mg BID	PIM447 100 mg QD+ Ruxolitinib 5 mg BID+LEE011 200 mg QD	PIM447 100 mg QD+ Ruxolitinib 10 mg BID+LEE011 200 mg QD
Number of Participants Analyzed [units: participants]	3	2	3	2
Plasma pharmacokinetics (PK) for LEE011 - Tmax (units: hr) Median (Full Range)				

Cycle 1 Day 1 (n=3,2,3,1)	1.00 (1.00 to 1.98)	3.00 (2.00 to 4.00)	1.98 (0.967 to 22.9)	1.00 (1.00 to 1.00)
Cycle 1 Day 15 (n=3,2,3,2)	1.08 (1.00 to 2.00)	3.00 (2.00 to 4.00)	1.00 (1.00 to 1.05)	2.00 (2.00 to 2.00)

Plasma pharmacokinetics (PK) for LEE011 - AUCinf

(Time Frame: Cycle 1 Day 1 and Cycle 1 Day 15)

	LEE011 200 mg QD+ Ruxolitinib 5 mg BID	**LEE011 200 mg QD+ Ruxolitinib 10 mg BID**	**PIM447 100 mg QD+ Ruxolitinib 5 mg BID+LEE011 200 mg QD**	**PIM447 100 mg QD+ Ruxolitinib 10 mg BID+LEE011 200 mg QD**
Arm/Group Description	LEE011 200 mg QD+ Ruxolitinib 5 mg BID	LEE011 200 mg QD+ Ruxolitinib 10 mg BID	PIM447 100 mg QD+ Ruxolitinib 5 mg BID+LEE011 200 mg QD	PIM447 100 mg QD+ Ruxolitinib 10 mg BID+LEE011 200 mg QD
Number of Participants Analyzed [units: participants]	1	1	1	1
Plasma pharmacokinetics (PK) for LEE011 - AUCinf (units: hr*ng/mL) Geometric Mean (Geometric Coefficient of Variation)				
Cycle 1 Day 1	2680 (NA%)[12345]	1920 (NA%)[12345]	1950 (NA%)[12345]	5180 (NA%)[12345]
Cycle 1 Day 15 (n=1,0,0,0)	3730 (NA%)[12345]			

[1] Geometric Coefficient of Variation is NA for n analyzed =1
[2] Geometric Coefficient of Variation is NA for n analyzed =1
[3] Geometric Coefficient of Variation is NA for n analyzed =1
[4] Geometric Coefficient of Variation is NA for n analyzed =1
[5] Geometric Coefficient of Variation is NA for n analyzed =1

Plasma pharmacokinetics (PK) for LEE011 - CL/F

(Time Frame: Cycle 1 Day 1 and Cycle 1 Day 15)

	LEE011 200 mg QD+ Ruxolitinib 5 mg BID	LEE011 200 mg QD+ Ruxolitinib 10 mg BID	PIM447 100 mg QD+ Ruxolitinib 5 mg BID+LEE011 200 mg QD	PIM447 100 mg QD+ Ruxolitinib 10 mg BID+LEE011 200 mg QD
Arm/Group Description	LEE011 200 mg QD+ Ruxolitinib 5 mg BID	LEE011 200 mg QD+ Ruxolitinib 10 mg BID	PIM447 100 mg QD+ Ruxolitinib 5 mg BID+LEE011 200 mg QD	PIM447 100 mg QD+ Ruxolitinib 10 mg BID+LEE011 200 mg QD
Number of Participants Analyzed [units: participants]	1	1	1	1
Plasma pharmacokinetics (PK) for LEE011 - CL/F (units: L/hr) Geometric Mean (Geometric Coefficient of Variation)				
Cycle 1 Day 1	74.6 (NA%)[12345]	104 (NA%)[12345]	103 (NA%)[12345]	38.6 (NA%)[12345]
Cycle 1 Day 15 (n=1,0,0,0)	53.6 (NA%)[12345]			

[1] Geometric Coefficient of Variation is NA for n analyzed =1
[2] Geometric Coefficient of Variation is NA for n analyzed =1
[3] Geometric Coefficient of Variation is NA for n analyzed =1
[4] Geometric Coefficient of Variation is NA for n analyzed =1
[5] Geometric Coefficient of Variation is NA for n analyzed =1

Plasma pharmacokinetics (PK) for LEE011 - Vz/F

(Time Frame: Cycle 1 Day 1 and Cycle 1 Day 15)

	LEE011 200 mg QD+ Ruxolitinib 5 mg BID	LEE011 200 mg QD+ Ruxolitinib 10 mg BID	PIM447 100 mg QD+ Ruxolitinib 5 mg BID+LEE011 200 mg QD	PIM447 100 mg QD+ Ruxolitinib 10 mg BID+LEE011 200 mg QD
Arm/Group Description	LEE011 200 mg QD+	LEE011 200 mg QD+ Ruxolitinib 10 mg BID	PIM447 100 mg QD+ Ruxolitinib 5 mg	PIM447 100 mg QD+ Ruxolitinib 10 mg

	Ruxolitinib 5 mg BID		BID+LEE011 200 mg QD	BID+LEE011 200 mg QD
Number of Participants Analyzed [units: participants]	1	1	1	1
Plasma pharmacokinetics (PK) for LEE011 - Vz/F (units: L) Geometric Mean (Geometric Coefficient of Variation)				
Cycle 1 Day 1	880 (NA%)[12345]	1240 (NA%)[12345]	1320 (NA%)[12345]	470 (NA%)[12345]
Cycle 1 Day 15 (n=1,0,0,0)	802 (NA%)[12345]			

[1] Geometric Coefficient of Variation is NA for n analyzed =1
[2] Geometric Coefficient of Variation is NA for n analyzed =1
[3] Geometric Coefficient of Variation is NA for n analyzed =1
[4] Geometric Coefficient of Variation is NA for n analyzed =1
[5] Geometric Coefficient of Variation is NA for n analyzed =1

Post-Hoc: All Collected Deaths

(Time Frame: On treatment deaths: up to Study Day 514; post-treatment death: occurred on Study Day 81.)

	PIM447 150 mg QD + Ruxolitinib 5 mg BID	**LEE011 200 mg QD+ Ruxolitinib 5 mg BID**	**LEE011 200 mg QD+ Ruxolitinib 10 mg BID**	**PIM447 100 mg QD+ Ruxolitinib 5 mg BID+LEE011 200 mg QD**	**PIM447 100 mg QD+ Ruxolitinib 10 mg BID+LEE011 200 mg QD**
Arm/Group Description	PIM447 150 mg QD + Ruxolitinib 5 mg BID	LEE011 200 mg QD+ Ruxolitinib 5 mg BID	LEE011 200 mg QD+ Ruxolitinib 10 mg BID	PIM447 100 mg QD+ Ruxolitinib 5 mg BID+LEE011 200 mg QD	PIM447 100 mg QD+ Ruxolitinib 10 mg BID+LEE011 200 mg QD
Number of Participants Analyzed [units: participants]	5	3	2	3	2

All Collected Deaths
(units: Participants)

Total Deaths	2	0	1	0	0
On-treatment Deaths	1	0	1	0	0

Safety Results

All-Cause Mortality

	PIM447 150 mg QD + Ruxolitinib 5 mg BID N = 5	LEE011 200 mg QD+ Ruxolitinib 5 mg BID N = 3	LEE011 200 mg QD+ Ruxolitinib 10 mg BID N = 2	PIM447 100 mg QD+ Ruxolitinib 5 mg BID+LEE011 200 mg QD N = 3	PPIM447 100 mg QD+ Ruxolitinib 10 mg BID+LEE011 200 mg QD N = 2	@All Patients@(RUX) N = 15
Arm/Group Description	PIM447 150 mg QD + Ruxolitinib 5 mg BID	LEE011 200 mg QD+ Ruxolitinib 5 mg BID	LEE011 200 mg QD+ Ruxolitinib 10 mg BID	PIM447 100 mg QD+ Ruxolitinib 5 mg BID+LEE011 200 mg QD	PIM447 100 mg QD+ Ruxolitinib 10 mg BID+LEE011 200 mg QD	@All Patients@(RUX)
Total participants affected	1 (20.00%)	0 (0.00%)	1 (50.00%)	0 (0.00%)	0 (0.00%)	2 (13.33%)

Serious Adverse Events by System Organ Class

Time Frame	Adverse events were reported from first dose of study treatment until end of study treatment plus 30 days post treatment, up to a maximum duration of 1933 days (approx 5.3 years).
Source Vocabulary for Table Default	MedDRA (23.0)
Assessment Type for Table Default	Systematic Assessment

	PIM447 150 mg QD + Ruxolitinib 5 mg BID N = 5	**LEE011 200 mg QD+ Ruxolitinib 5 mg BID N = 3**	**LEE011 200 mg QD+ Ruxolitinib 10 mg BID N = 2**	**PIM447 100 mg QD+ Ruxolitinib 5 mg BID+LEE011 200 mg QD N = 3**	**PPIM447 100 mg QD+ Ruxolitinib 10 mg BID+LEE011 200 mg QD N = 2**	**@All Patients@(RUX) N = 15**
Arm/Group Description	PIM447 150 mg QD + Ruxolitinib 5 mg BID	LEE011 200 mg QD+ Ruxolitinib 5 mg BID	LEE011 200 mg QD+ Ruxolitinib 10 mg BID	PIM447 100 mg QD+ Ruxolitinib 5 mg BID+LEE011 200 mg QD	PIM447 100 mg QD+ Ruxolitinib 10 mg BID+LEE011 200 mg QD	@All Patients@(RUX)
Total participants affected	4 (80.00%)	1 (33.33%)	1 (50.00%)	2 (66.67%)	2 (100.00%)	10 (66.67%)
Blood and lymphatic system disorders						
Anaemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (33.33%)	1 (50.00%)	2 (13.33%)
Febrile neutropenia	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)
Cardiac disorders						
Atrial fibrillation	0 (0.00%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)
Gastrointestinal disorders						

Dieulafoy's vascular malformation	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (50.00%)	1 (6.67%)
Infections and infestations						
Gastroenteritis	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)
Gastroenteritis viral	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)
Pneumococcal sepsis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (50.00%)	1 (6.67%)
Pneumonia	2 (40.00%)	0 (0.00%)	1 (50.00%)	0 (0.00%)	0 (0.00%)	3 (20.00%)
Sepsis	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)
Metabolism and nutrition disorders						
Dehydration	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)
Psychiatric disorders						
Delirium	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (33.33%)	0 (0.00%)	1 (6.67%)
Renal and urinary disorders						
Chronic kidney disease	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)
Respiratory, thoracic and mediastinal disorders						
Lung disorder	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)

Other Adverse Events by System Organ Class

Time Frame	Adverse events were reported from first dose of study treatment until end of study treatment plus 30 days post treatment, up to a maximum duration of 1933 days (approx 5.3 years).
Source Vocabulary for Table Default	MedDRA (23.0)

Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	0%

	PIM447 150 mg QD + Ruxolitinib 5 mg BID N = 5	**LEE011 200 mg QD+ Ruxolitinib 5 mg BID N = 3**	**LEE011 200 mg QD+ Ruxolitinib 10 mg BID N = 2**	**PIM447 100 mg QD+ Ruxolitinib 5 mg BID+LEE011 200 mg QD N = 3**	**PPIM447 100 mg QD+ Ruxolitinib 10 mg BID+LEE011 200 mg QD N = 2**	**@All Patients@(RUX) N = 15**
Arm/Group Description	PIM447 150 mg QD + Ruxolitinib 5 mg BID	LEE011 200 mg QD+ Ruxolitinib 5 mg BID	LEE011 200 mg QD+ Ruxolitinib 10 mg BID	PIM447 100 mg QD+ Ruxolitinib 5 mg BID+LEE011 200 mg QD	PIM447 100 mg QD+ Ruxolitinib 10 mg BID+LEE011 200 mg QD	@All Patients@(RUX)
Total participants affected	5 (100.00%)	3 (100.00%)	2 (100.00%)	3 (100.00%)	2 (100.00%)	15 (100.00%)
Blood and lymphatic system disorders						
Anaemia	2 (40.00%)	2 (66.67%)	1 (50.00%)	3 (100.00%)	2 (100.00%)	10 (66.67%)
Leukopenia	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)
Lymphopenia	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (50.00%)	2 (13.33%)
Neutropenia	1 (20.00%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	1 (50.00%)	3 (20.00%)
Thrombocytopenia	2 (40.00%)	1 (33.33%)	1 (50.00%)	1 (33.33%)	2 (100.00%)	7 (46.67%)
Cardiac disorders						
Atrial fibrillation	0 (0.00%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)
Ear and labyrinth disorders						
Vertigo positional	0 (0.00%)	0 (0.00%)	1 (50.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)

Eye disorders						
Conjunctival haemorrhage	0 (0.00%)	0 (0.00%)	1 (50.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)
Vision blurred	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (50.00%)	1 (6.67%)
Gastrointestinal disorders						
Abdominal discomfort	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (33.33%)	0 (0.00%)	1 (6.67%)
Abdominal distension	0 (0.00%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	1 (50.00%)	2 (13.33%)
Abdominal pain	2 (40.00%)	0 (0.00%)	1 (50.00%)	0 (0.00%)	1 (50.00%)	4 (26.67%)
Abdominal pain upper	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (33.33%)	0 (0.00%)	1 (6.67%)
Anal inflammation	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)
Aphthous ulcer	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)
Constipation	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (50.00%)	1 (6.67%)
Diarrhoea	2 (40.00%)	1 (33.33%)	0 (0.00%)	1 (33.33%)	0 (0.00%)	4 (26.67%)
Dyspepsia	2 (40.00%)	0 (0.00%)	0 (0.00%)	1 (33.33%)	1 (50.00%)	4 (26.67%)
Gastrointestinal angiectasia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (50.00%)	1 (6.67%)
Haemorrhoidal haemorrhage	0 (0.00%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)
Mouth ulceration	0 (0.00%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)
Nausea	1 (20.00%)	1 (33.33%)	0 (0.00%)	1 (33.33%)	1 (50.00%)	4 (26.67%)
Stomatitis	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (50.00%)	2 (13.33%)
Toothache	0 (0.00%)	0 (0.00%)	1 (50.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)
Vomiting	2 (40.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (13.33%)
General disorders and administration site conditions						

Asthenia	0 (0.00%)	0 (0.00%)	1 (50.00%)	0 (0.00%)	1 (50.00%)	2 (13.33%)
Early satiety	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (50.00%)	1 (6.67%)
Fatigue	3 (60.00%)	3 (100.00%)	0 (0.00%)	1 (33.33%)	1 (50.00%)	8 (53.33%)
Feeling cold	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (50.00%)	1 (6.67%)
Mucosal dryness	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (50.00%)	1 (6.67%)
Mucosal inflammation	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)
Oedema peripheral	0 (0.00%)	1 (33.33%)	1 (50.00%)	0 (0.00%)	2 (100.00%)	4 (26.67%)
Pyrexia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (50.00%)	1 (6.67%)
Infections and infestations						
Bronchitis	0 (0.00%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)
Chest wall abscess	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)
Conjunctivitis	0 (0.00%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)
Cystitis	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)
Erysipelas	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (33.33%)	0 (0.00%)	1 (6.67%)
Herpes virus infection	0 (0.00%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)
Herpes zoster	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (33.33%)	0 (0.00%)	1 (6.67%)
Influenza	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (33.33%)	0 (0.00%)	1 (6.67%)
Nasopharyngitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (50.00%)	1 (6.67%)
Respiratory tract infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (50.00%)	1 (6.67%)
Tinea versicolour	0 (0.00%)	0 (0.00%)	1 (50.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)
Tooth abscess	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)
Injury, poisoning and procedural complications						
Fall	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (33.33%)	0 (0.00%)	1 (6.67%)

Tooth fracture	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (50.00%)	1 (6.67%)
Transfusion reaction	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (50.00%)	1 (6.67%)
Investigations						
Alanine aminotransferase increased	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)
Aspartate aminotransferase increased	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)
Blood alkaline phosphatase increased	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)
Blood creatine phosphokinase increased	0 (0.00%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)
Blood creatinine increased	0 (0.00%)	0 (0.00%)	2 (100.00%)	0 (0.00%)	0 (0.00%)	2 (13.33%)
Blood uric acid increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (33.33%)	0 (0.00%)	1 (6.67%)
Breath sounds abnormal	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (50.00%)	1 (6.67%)
Gamma-glutamyltransferase increased	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)
Lymphocyte count decreased	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (66.67%)	0 (0.00%)	2 (13.33%)
Platelet count decreased	2 (40.00%)	0 (0.00%)	0 (0.00%)	1 (33.33%)	0 (0.00%)	3 (20.00%)
Weight decreased	1 (20.00%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	1 (50.00%)	3 (20.00%)
Metabolism and nutrition disorders						
Decreased appetite	1 (20.00%)	2 (66.67%)	0 (0.00%)	0 (0.00%)	1 (50.00%)	4 (26.67%)
Hyperkalaemia	2 (40.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (13.33%)

Hyperuricaemia	0 (0.00%)	1 (33.33%)	1 (50.00%)	0 (0.00%)	0 (0.00%)	2 (13.33%)
Hypoalbuminaemia	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)
Hypocalcaemia	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)
Hypomagnesaemia	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)
Hyponatraemia	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)
Musculoskeletal and connective tissue disorders						
Arthralgia	0 (0.00%)	2 (66.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (13.33%)
Bone pain	0 (0.00%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	1 (50.00%)	2 (13.33%)
Bursitis	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)
Jaw disorder	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (50.00%)	1 (6.67%)
Joint stiffness	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (50.00%)	1 (6.67%)
Muscle spasms	0 (0.00%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	1 (50.00%)	2 (13.33%)
Neck pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (50.00%)	1 (6.67%)
Osteoarthritis	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)
Pain in extremity	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)
Nervous system disorders						
Ageusia	0 (0.00%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)
Dizziness	1 (20.00%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	1 (50.00%)	3 (20.00%)
Headache	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (33.33%)	0 (0.00%)	1 (6.67%)
Sciatica	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)
Somnolence	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (33.33%)	0 (0.00%)	1 (6.67%)
Tremor	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (33.33%)	0 (0.00%)	1 (6.67%)
Psychiatric disorders						

Confusional state	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (33.33%)	0 (0.00%)	1 (6.67%)
Renal and urinary disorders						
Pollakiuria	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)
Renal failure	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)
Respiratory, thoracic and mediastinal disorders						
Cough	0 (0.00%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)
Dyspnoea	0 (0.00%)	3 (100.00%)	1 (50.00%)	0 (0.00%)	0 (0.00%)	4 (26.67%)
Epistaxis	0 (0.00%)	1 (33.33%)	0 (0.00%)	1 (33.33%)	0 (0.00%)	2 (13.33%)
Interstitial lung disease	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (50.00%)	1 (6.67%)
Productive cough	0 (0.00%)	0 (0.00%)	1 (50.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)
Sinus pain	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)
Skin and subcutaneous tissue disorders						
Alopecia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (50.00%)	1 (6.67%)
Dermatitis acneiform	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)
Dry skin	0 (0.00%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)
Erythema	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (50.00%)	1 (6.67%)
Hyperhidrosis	0 (0.00%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)
Nail disorder	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (33.33%)	0 (0.00%)	1 (6.67%)
Night sweats	0 (0.00%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	1 (50.00%)	2 (13.33%)
Petechiae	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (50.00%)	2 (13.33%)
Pruritus	0 (0.00%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)
Rash	1 (20.00%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	1 (50.00%)	3 (20.00%)
Rash maculo-papular	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (33.33%)	0 (0.00%)	1 (6.67%)

Skin lesion	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)
Vascular disorders						
Arterial disorder	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)
Haematoma	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (50.00%)	1 (6.67%)
Hot flush	0 (0.00%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	1 (50.00%)	2 (13.33%)
Phlebitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (33.33%)	0 (0.00%)	1 (6.67%)
Vascular stenosis	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)

Conclusion:

This study was terminated early after 15 patients were recruited in the dose escalation portion of the study, before determination of Maximum tolerated dose (MTD)(s)/ Recommended dose for expansion (RDE)(s) in any of the combination treatment arms, due to factors including unfavorable hematologic toxicity and challenges in recruitment. Preliminary Pharmacokinetic(s) (PK) and efficacy data should be interpreted with caution with such a limited dataset.

Date of Clinical Trial Report

18-Aug-21