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Sponsor

Novartis

Generic Drug Name

Ruxolitinib, siremadlin, crizanlizumab, sabatolimab, rineterkib, NIS793

Trial Indication

Myelofibrosis

Protocol Number

CINC424H12201

Protocol Title

A randomized, open-label, phase I/II open platform study evaluating safety and efficacy of novel ruxolitinib combinations in myelofibrosis patients

Clinical Trial Phase

Phase 1/Phase 2

Phase of Drug Development

Phase III

Study Start/End Dates

Study Start Date: September 26, 2019 (Actual)

Primary Completion Date: May 03, 2023 (Actual)
Study Completion Date: August 28, 2024 (Actual)

Reason for Termination

Sponsor decision

Study Design/Methodology

This open-label, multi-center, Phase Ib/II platform study design consisted of 3 parts. Part 1 was a Phase Ib dose escalation and safety run-in for the 5 novel agents in combination with ruxolitinib to assess safety, tolerability and to confirm a recommended Phase II dose. Dose escalation cohorts were treated with ruxoltinib + siremadlin or ruxolitinib + rineterkib. Safety run-in cohorts were treated with either ruxolitinb + sabatolimab, ruxolitinb + crizanlizumab or ruxolitinib + NIS793.

Parts 2 and 3 were Phase II selection and expansion, respectively, to assess preliminary efficacy of the combination treatments from Part 1 that were evaluated as safe and tolerable. The number of combination treatment arms opening in Part 2 depended on the results of Part 1. In Part 2, an interim analysis was planned to determine if combination treatment(s) could be expanded in Part 3.

In June 2022, Novartis decided to permanently halt the study enrollment in all ongoing parts (Part 1 and Part 2), and Part 3 (expansion) was not initiated. With Protocol Amendment 8, an extension treatment phase of 12 cycles was added in Part 1 to allow access to the combination treatment for ongoing subjects deriving clinical benefit. In consideration of the enrollment halt, Parts 2 and 3 objectives were not pursued, and Part 1 objectives were updated accordingly.

Centers

22 centers in 13 countries: Australia(3), Spain(4), Germany(4), Hungary(1), Netherlands(1), Switzerland(2), United Kingdom(1), Denmark(1), Italy(1), Sweden(1), Canada(1), Russia(1), Turkey(1)

Objectives:

Primary Objective:

- To characterize the safety, tolerability, and recommended Phase 2 dose (RP2D) of each combination partner used with ruxolitinib (Part 1 core).

Secondary Objectives:

- To evaluate changes in symptoms of myelofibrosis in each treatment arm using Myelofibrosis Symptom Assessment Form MFSAF v4.0 (Part 1 core).
- To characterize the pharmacokinetic (PK) profile of ruxolitinib administered in combination with siremadlin, crizanlizumab, sabatolimab, rineterkib and NIS793, respectively (Part 1 core).
- To evaluate the changes in spleen size in each treatment arm (Part 1 core and extension).
- To evaluate long-term safety and tolerability of ruxolitinib combination treatments in each arm (Part 1 core and extension).

Test Products, Doses, and Modes of Administration

Oral tablets of ruxolitinib 5 mg; oral capsules of siremadlin 10 mg, 20 mg, or 40 mg; intravenous infusion of crizanlizumab 100 mg/10 mL; intravenous infusion of sabatolimab 100 mg/mL or 400 mg/4 mL; oral capsules of rineterkib 100 mg; intravenous infusion of NIS793 700 mg/7 mL.

Statistical Methods

The following analysis sets were used in this trial:

- The full analysis set (FAS) comprised all participants who received any study drug.
- The safety set included all participants who received at least one dose of study treatment.
- The dose determining set (DDS) included all participants from the safety run-in and dose escalation part (Part 1) of the study who met the minimum exposure criterion and had sufficient safety evaluations or experienced a dose limiting toxicity (DLT) between C1D1 and C3D1.
- The PK analysis set included all enrolled participants who had an evaluable PK profile.

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Study Population: Key Inclusion/Exclusion Criteria

Core treatment phase Inclusion Criteria:

• Subjects have diagnosis of primary myelofibrosis (PMF) according to the 2016 World Health Organization (WHO) criteria, or diagnosis of post-essential thrombocythemia (ET) (PET-MF) or post-polycythemia vera (PV) myelofibrosis (PPV-MF) according to the International Working Group for Myelofibrosis Research and Treatment (IWG-MRT) 2007 criteria

• Palpable spleen of at least 5 cm from the left costal margin (LCM) to the point of greatest splenic protrusion or enlarged spleen volume of at least 450 cm3 per MRI or CT scan at baseline (a MRI/CT scan up to 8 weeks prior to first dose of study treatment can be accepted).

• Have been treated with ruxolitinib for at least 12 weeks prior to first dose of study treatment

• Are stable (no dose adjustments) on the prescribed ruxolitinib dose (between 5 and 25 mg twice a day (BID)) for ≥ 4 weeks prior to first dose of study treatment

Extension treatment phase inclusion criteria:

-Signed consent for the extension treatment phase

-ongoing in the core treatment phase

- demonstrates clinical benefit of treatment in core treatment phase per investigator's assessment.

Core treatment phase Exclusion Criteria:

• Not able to understand and to comply with study instructions and requirements.

• Received any investigational agent for the treatment of MF (except ruxolitinib) within 30 days of first dose of study treatment or within 5 half-lives of the study treatment, whichever is greater

• Peripheral blood blasts count of > 10%.

• has documented severe hypersensitivity reactions/immunogenicity (IG) to a prior biologic product or Received a monoclonal

antibody (Ab) or immunoglobulin-based agent within 1 year of screening in NIS793, crizanlizumab or sabatolimab arms, or in rineterkib or siremadlin arms within <=4 weeks of screening or <=5 half-lives whichever is shorter

• Splenic irradiation within 6 months prior to the first dose of study drug

• Received blood platelet transfusion within 28 days prior to first dose of study treatment.

Extension treatment phase Exclusion Criteria:

- meets any of study treatment discontinuation criteria

- current evidence of treatment failure per investigator, following treatment in core treatment phase

- enrolled in another interventional study

-evidence of non-compliance to study procedures or withdrew consent in core treatment phase

-currently has unresolved toxicities for which study treatment has been interrupted in the core treatment phase

-local access to alternative myelofibrosis treatment including those currently under investigation in clinical trials as assessed suitable in the opinion of the investigator.

Participant Flow Table

Overall Study

	Part 1: Ruxolitinib + Siremadlin 20 mg	Part 1: Ruxolitinib + Siremadlin 30 mg	Part 1: Ruxolitinib + Siremadlin 40 mg	Part 1: Ruxolitinib + Rineterkib 200 mg	Part 1: Ruxolitinib + Crizanlizumab	Part 1: Ruxolitinib + Sabatolimab	Part 1: Ruxolitinib + NIS793	Part 2: Ruxolitinib	Total
Arm/Group Description	Dose escalation of siremadlin added to existing	Dose escalation of siremadlin added to existing	Dose escalation of siremadlin added to existing	Dose escalation of rineterkib added to existing	Safety run-in of crizanlizumab added to existing stable dose of ruxolitinib	Safety run-in of sabatolimab added to existing	Safety run-in of NIS793 added to existing stable dose of ruxolitinib	Existing stable dose of ruxolitinib as control for Part 2	

	stable dose of ruxolitinib	stable dose of ruxolitinib	stable dose of ruxolitinib	stable dose of ruxolitinib		stable dose of ruxolitinib			
Started	7	10	6	9	6	2	4	1	45
Completed	6	8	2	6	4	0	3	0	29
Not Completed	1	2	4	3	2	2	1	1	16
Subject Decision	0	0	0	1	2	2	0	1	6
Death	0	0	3	1	0	0	0	0	4
Physician Decision	1	2	0	0	0	0	0	0	3
Adverse Event	0	0	1	1	0	0	0	0	2
New Therapy For Study Indication	0	0	0	0	0	0	1	0	1

Baseline Characteristics

	Part 1: Ruxolitinib + Siremadlin 20 mg	**Part 1: Ruxolitinib + Siremadlin 30 mg**	**Part 1: Ruxolitinib + Siremadlin 40 mg**	**Part 1: Ruxolitinib + Rineterkib 200 mg**	**Part 1: Ruxolitinib + Crizanlizumab**	**Part 1: Ruxolitinib + Sabatolimab**	**Part 1: Ruxolitinib + NIS793**	**Part 2: Ruxolitinib**	**Total**
Arm/Group Description	Dose escalation of siremadlin added to existing	Dose escalation of siremadlin added to existing	Dose escalation of siremadlin added to existing	Dose escalation of rineterkib added to existing stable dose of ruxolitinib	Safety run-in of crizanlizumab added to existing stable dose of ruxolitinib	Safety run-in of sabatolimab added to existing stable dose of ruxolitinib	Safety run-in of NIS793 added to existing stable dose of ruxolitinib	Existing stable dose of ruxolitinib as control for Part 2	

	stable dose of ruxolitinib	stable dose of ruxolitinib	stable dose of ruxolitinib						
Number of Participants [units: participants]	7	10	6	9	6	2	4	0	44
Baseline Analysis Population Description	The full analysis set included all subjects who received any study drug. Part 2 enrollment included 1 participant. Data are not reported for this participant in order to protect participant privacy and confidentiality.								
Age Continuous (units: years) Analysis Population Type: Participants Mean ± Standard Deviation									
	70.6±6.5	62.3±10.7	74.3±9.9	67.3±7.8	65.0±8.1	62.5±12.0	70.8±7.3		67.4±9.2
Age, Customized (units: participants) Analysis Population Type: Participants Count of Participants (Not Applicable)									
<65	1	5	1	4	4	1	1		17
>=65	6	5	5	5	2	1	3		27
Sex: Female, Male (units: participants) Analysis Population Type: Participants Count of Participants (Not Applicable)									
Female	2	6	0	2	1	0	1		12
Male	5	4	6	7	5	2	3		32
Race/Ethnicity, Customized (units: participants) Analysis Population Type: Participants Count of Participants (Not Applicable)									
White	7	10	6	8	5	2	4		42
Unknown	0	0	0	1	1	0	0		2

Primary Outcome Results

Incidence and Severity of Dose Limiting Toxicities Within the First 2 Cycles in Part 1

Description	Incidence and severity of dose limiting toxicities within the first 2 cycles (6 or 8 weeks) in Part 1 of the study. DLTs were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) criteria Version 5.0. Grade 0 was assigned for all non-missing values not graded as 1 or higher. Higher grade indicated more severity. Grade 5 was not used.
Time Frame	Baseline to the end of Cycle 2 (6 or 8 weeks)
Analysis Population Description	The dose-determining set included all subjects from the safety run-in and dose escalation part (Part 1) of the study who met the minimum exposure criterion and had sufficient safety evaluations or experienced a DLT between C1D1 and C3D1.

	Part 1: Ruxolitinib + Siremadlin 20 mg	**Part 1: Ruxolitinib + Siremadlin 30 mg**	**Part 1: Ruxolitinib + Siremadlin 40 mg**	**Part 1: Ruxolitinib + Rineterkib 200 mg**	**Part 1: Ruxolitinib + Crizanlizumab**	**Part 1: Ruxolitinib + Sabatolimab**	**Part 1: Ruxolitinib + NIS793**
Arm/Group Description	Dose escalation of siremadlin added to existing stable dose of ruxolitinib	Dose escalation of siremadlin added to existing stable dose of ruxolitinib	Dose escalation of siremadlin added to existing stable dose of ruxolitinib	Dose escalation of rineterkib added to existing stable dose of ruxolitinib	Safety run-in of crizanlizumab added to existing stable dose of ruxolitinib	Safety run-in of sabatolimab added to existing stable dose of ruxolitinib	Safety run-in of NIS793 added to existing stable dose of ruxolitinib
Number of Participants Analyzed [units: participants]	6	7	5	9	5	2	0
Incidence and Severity of Dose Limiting Toxicities Within the First 2 Cycles in Part 1 (units: participants)							
Grade 3	0	0	1	1	0	0	
Grade 4	0	1	1	0	0	0	

Response Rate at the End of Cycle 6 or Cycle 8 in Part 1

Description	Composite of anemia improvement (hemoglobin level) and no spleen volume progression and no symptom worsening in Part 2 and Part 3 of the study. For a subject to be considered a responder, all three components of the composite had to be fulfilled.
Time Frame	Baseline to the end of Cycle 6 or 8 (24 weeks)
Analysis Population Description	Enrollment was permanently halted; therefore, data were not collected for this outcome measure.

	Part 1: Ruxolitinib + Siremadlin 20 mg	Part 1: Ruxolitinib + Siremadlin 30 mg	Part 1: Ruxolitinib + Siremadlin 40 mg	Part 1: Ruxolitinib + Rineterkib 200 mg	Part 1: Ruxolitinib + Crizanlizumab	Part 1: Ruxolitinib + Sabatolimab	Part 1: Ruxolitinib + NIS793
Arm/Group Description	Dose escalation of siremadlin added to existing stable dose of ruxolitinib	Dose escalation of siremadlin added to existing stable dose of ruxolitinib	Dose escalation of siremadlin added to existing stable dose of ruxolitinib	Dose escalation of rineterkib added to existing stable dose of ruxolitinib	Safety run-in of crizanlizumab added to existing stable dose of ruxolitinib	Safety run-in of sabatolimab added to existing stable dose of ruxolitinib	Safety run-in of NIS793 added to existing stable dose of ruxolitinib
Number of Participants Analyzed [units: participants]	0	0	0	0	0	0	0
Response Rate at the End of Cycle 6 or Cycle 8 in Part 1 (units: percentage of participants)							

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Secondary Outcome Results

Percentage of Subjects Achieving an Improvement in Hemoglobin Level of ≥ 1.5 g/dL From Baseline in Part 1

Description

Time Frame: Week 24, Week 48

Analysis Population Description: The full analysis set included all subjects who received any study drug.

	Part 1: Ruxolitinib + Siremadlin 20 mg	Part 1: Ruxolitinib + Siremadlin 30 mg	Part 1: Ruxolitinib + Siremadlin 40 mg	Part 1: Ruxolitinib + Rineterkib 200 mg	Part 1: Ruxolitinib + Crizanlizumab	Part 1: Ruxolitinib + Sabatolimab	Part 1: Ruxolitinib + NIS793
Arm/Group Description	Dose escalation of siremadlin added to existing stable dose of ruxolitinib	Dose escalation of siremadlin added to existing stable dose of ruxolitinib	Dose escalation of siremadlin added to existing stable dose of ruxolitinib	Dose escalation of rineterkib added to existing stable dose of ruxolitinib	Safety run-in of crizanlizumab added to existing stable dose of ruxolitinib	Safety run-in of sabatolimab added to existing stable dose of ruxolitinib	Safety run-in of NIS793 added to existing stable dose of ruxolitinib
Number of Participants Analyzed [units: participants]	7	10	6	9	6	2	4
Percentage of Subjects Achieving an Improvement in Hemoglobin Level of ≥ 1.5 g/dL From Baseline in Part 1 (units: percentage of participants)							
Week 24	0	0	0	11.1	16.7	0	0
Week 48	0	0	0	11.1	0	0	0

Percentage of Subjects Achieving an Improvement in Hemoglobin Level of at Least >= 2.0 g/dL From Baseline in Part 1

Description

Time Frame: Week 24, Week 48

Analysis Population Description: The full analysis set included all subjects who received any study drug.

	Part 1: Ruxolitinib + Siremadlin 20 mg	Part 1: Ruxolitinib + Siremadlin 30 mg	Part 1: Ruxolitinib + Siremadlin 40 mg	Part 1: Ruxolitinib + Rineterkib 200 mg	Part 1: Ruxolitinib + Crizanlizumab	Part 1: Ruxolitinib + Sabatolimab	Part 1: Ruxolitinib + NIS793
Arm/Group Description	Dose escalation of siremadlin added to existing stable dose of ruxolitinib	Dose escalation of siremadlin added to existing stable dose of ruxolitinib	Dose escalation of siremadlin added to existing stable dose of ruxolitinib	Dose escalation of rineterkib added to existing stable dose of ruxolitinib	Safety run-in of crizanlizumab added to existing stable dose of ruxolitinib	Safety run-in of sabatolimab added to existing stable dose of ruxolitinib	Safety run-in of NIS793 added to existing stable dose of ruxolitinib
Number of Participants Analyzed [units: participants]	7	10	6	9	6	2	4
Percentage of Subjects Achieving an Improvement in Hemoglobin Level of at Least >= 2.0 g/dL From Baseline in Part 1 (units: percentage of participants)							
Week 24	0	0	0	11.1	0	0	0
Week 48	0	0	0	11.1	0	0	0

Change in Spleen Length From Baseline in Part 1

Description: Change in spleen length measured in centimeters by manual palpation.

Time Frame: Baseline, Week 24, Week 48

Analysis Population Description	The full analysis set included all subjects who received any study drug.

	Part 1: Ruxolitinib + Siremadlin 20 mg	Part 1: Ruxolitinib + Siremadlin 30 mg	Part 1: Ruxolitinib + Siremadlin 40 mg	Part 1: Ruxolitinib + Rineterkib 200 mg	Part 1: Ruxolitinib + Crizanlizumab	Part 1: Ruxolitinib + Sabatolimab	Part 1: Ruxolitinib + NIS793
Arm/Group Description	Dose escalation of siremadlin added to existing stable dose of ruxolitinib	Dose escalation of siremadlin added to existing stable dose of ruxolitinib	Dose escalation of siremadlin added to existing stable dose of ruxolitinib	Dose escalation of rineterkib added to existing stable dose of ruxolitinib	Safety run-in of crizanlizumab added to existing stable dose of ruxolitinib	Safety run-in of sabatolimab added to existing stable dose of ruxolitinib	Safety run-in of NIS793 added to existing stable dose of ruxolitinib
Number of Participants Analyzed [units: participants]	6	8	4	4	4	0	0
Change in Spleen Length From Baseline in Part 1 (units: centimeters)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
Week 24 n=6,8,4,4,4,0,0	-3.3 ± 2.6	-5.5 ± 3.9	-6.3 ± 4.6	-1.8 ± 3.9	-1.5 ± 1.9		
Week 48 n=2,1,2,1,1,0,0	-5.0 ± 0.0	-9.0 ± NA[1]	-6.0 ± 7.1	-8.0 ± NA[1]	-5.0 ± NA[1]		

[1] Standard deviation was not calculable due to the single data point.

Percentage of Subjects With >=35% Reduction in Spleen Volume From Baseline in Part 1

Description	Change in spleen volume measured by magnetic resonance imaging (MRI) or computed tomography (CT) from baseline.
Time Frame	Week 24, Week 48
Analysis Population Description	The full analysis set included all subjects who received any study drug.

	Part 1: Ruxolitinib + Siremadlin 20 mg	Part 1: Ruxolitinib + Siremadlin 30 mg	Part 1: Ruxolitinib + Siremadlin 40 mg	Part 1: Ruxolitinib + Rineterkib 200 mg	Part 1: Ruxolitinib + Crizanlizumab	Part 1: Ruxolitinib + Sabatolimab	Part 1: Ruxolitinib + NIS793
Arm/Group Description	Dose escalation of siremadlin added to existing stable dose of ruxolitinib	Dose escalation of siremadlin added to existing stable dose of ruxolitinib	Dose escalation of siremadlin added to existing stable dose of ruxolitinib	Dose escalation of rineterkib added to existing stable dose of ruxolitinib	Safety run-in of crizanlizumab added to existing stable dose of ruxolitinib	Safety run-in of sabatolimab added to existing stable dose of ruxolitinib	Safety run-in of NIS793 added to existing stable dose of ruxolitinib
Number of Participants Analyzed [units: participants]	7	10	6	9	6	2	4
Percentage of Subjects With >=35% Reduction in Spleen Volume From Baseline in Part 1 (units: percentage of participants)							
Week 24	14.3	60.0	0	0	0	0	0
Week 48	14.3	10.0	16.7	0	0	0	0

Percentage of Subjects With >=25% Reduction in Spleen Volume From Baseline in Part 1

Description	Change in spleen volume measured by magnetic resonance imaging (MRI) or computed tomography (CT) from baseline.
Time Frame	Week 24, Week 48
Analysis Population Description	The full analysis set included all subjects who received any study drug.

	Part 1: Ruxolitinib + Siremadlin 20 mg	Part 1: Ruxolitinib + Siremadlin 30 mg	Part 1: Ruxolitinib + Siremadlin 40 mg	Part 1: Ruxolitinib + Rineterkib 200 mg	Part 1: Ruxolitinib + Crizanlizumab	Part 1: Ruxolitinib + Sabatolimab	Part 1: Ruxolitinib + NIS793
Arm/Group Description	Dose escalation of siremadlin	Dose escalation of siremadlin	Dose escalation of siremadlin	Dose escalation of rineterkib	Safety run-in of crizanlizumab added to	Safety run-in of sabatolimab added to	Safety run-in of NIS793 added to existing

	added to existing stable dose of ruxolitinib	added to existing stable dose of ruxolitinib	added to existing stable dose of ruxolitinib	added to existing stable dose of ruxolitinib	existing stable dose of ruxolitinib	existing stable dose of ruxolitinib	stable dose of ruxolitinib
Number of Participants Analyzed [units: participants]	7	10	6	9	6	2	4
Percentage of Subjects With >=25% Reduction in Spleen Volume From Baseline in Part 1 (units: percentage of participants)							
Week 24	28.6	60.0	0	11.1	0	0	0
Week 48	28.6	10.0	16.7	11.1	0	0	0

Percentage of Subjects in Part 1 With >=50% Reduction From Baseline in Myelofibrosis Symptom Assessment Form, Version 4.0 (MFSAF v4.0)

Description	The MFSAF v4.0 questionnaire focuses on the 7 core symptoms of MF: fatigue, night sweats, pruritus, abdominal discomfort, pain under the ribs on the left side, early satiety and bone pain. Subjects record symptom severity at it worst for each of the 7 symptoms on an 11-point numeric rating scale, from 0 (absent) to 10 (worst imaginable). The Total Symptom Score (TSS) is the sum of all the scores for all 7 symptoms.
Time Frame	Week 12, Week 24, Week 48
Analysis Population Description	The full analysis set included all subjects who received any study drug.

	Part 1: Ruxolitinib + Siremadlin 20 mg	**Part 1: Ruxolitinib + Siremadlin 30 mg**	**Part 1: Ruxolitinib + Siremadlin 40 mg**	**Part 1: Ruxolitinib + Rineterkib 200 mg**	**Part 1: Ruxolitinib + Crizanlizumab**	**Part 1: Ruxolitinib + Sabatolimab**	**Part 1: Ruxolitinib + NIS793**
Arm/Group Description	Dose escalation of siremadlin added to existing stable	Dose escalation of siremadlin added to existing stable	Dose escalation of siremadlin added to existing stable	Dose escalation of rineterkib added to existing stable	Safety run-in of crizanlizumab added to existing stable dose of ruxolitinib	Safety run-in of sabatolimab added to existing stable dose of ruxolitinib	Safety run-in of NIS793 added to existing stable dose of ruxolitinib

	dose of ruxolitinib	dose of ruxolitinib	dose of ruxolitinib	dose of ruxolitinib			
Number of Participants Analyzed [units: participants]	7	10	6	9	6	2	4
Percentage of Subjects in Part 1 With >=50% Reduction From Baseline in Myelofibrosis Symptom Assessment Form, Version 4.0 (MFSAF v4.0) (units: percentage of participants)							
Week 12	42.9	30.0	16.7	11.1	16.7	0	0
Week 24	14.3	20.0	33.3	11.1	16.7	0	0
Week 48	14.3	10.0	16.7	0	0	0	0

Area Under the Plasma Concentration Versus Time Curve From Time Zero to the Last Measurable Concentration Sampling Time (AUClast) for Siremadlin, Rineterkib, Crizanlizumab, Sabatolimab, and NIS793 in Part 1

Description

Time Frame: Days 1 and 5 of Cycles 1 and 2 for siremadlin and Cycles 1 and 3 for crizanlizumab, sabatolimab, and NIS793; Days 1 and 15 of Cycle 1 for rineterkib

Analysis Population Description: The pharmacokinetic (PK) analysis set included all enrolled subjects who had an evaluable PK profile.

	Part 1: Ruxolitinib + Siremadlin 20 mg (AUClast for Siremadlin)	**Part 1: Ruxolitinib + Siremadlin 30 mg (AUClast for Siremadlin)**	**Part 1: Ruxolitinib + Siremadlin 40 mg (AUClast for Siremadlin)**	**Part 1: Ruxolitinib + Rineterkib 200 mg (AUClast for Rineterkib)**	**Part 1: Ruxolitinib + Crizanlizumab (AUClast for Crizanlizumab)**	**Part 1: Ruxolitinib + Sabatolimab (AUClast for Sabatolimab)**	**Part 1: Ruxolitinib + NIS793 (AUClast for NIS793)**
Arm/Group Description	Dose escalation of siremadlin added to existing stable	Dose escalation of siremadlin added to existing stable	Dose escalation of siremadlin added to existing stable	Dose escalation of rineterkib added to existing stable	Safety run-in of crizanlizumab added to existing stable dose of ruxolitinib	Safety run-in of sabatolimab added to existing stable	Safety run-in of NIS793 added to existing stable dose of ruxolitinib

	dose of ruxolitinib	dose of ruxolitinib	dose of ruxolitinib	dose of ruxolitinib		dose of ruxolitinib	
Number of Participants Analyzed [units: participants]	6	9	5	9	5	2	4
Area Under the Plasma Concentration Versus Time Curve From Time Zero to the Last Measurable Concentration Sampling Time (AUClast) for Siremadlin, Rineterkib, Crizanlizumab, Sabatolimab, and NIS793 in Part 1 (units: ng*hr/mL)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
Cycle 1 Day 1 n=6,9,5,9,5,2,4	1520 ± 619	2560 ± 1530	3780 ± 1840	6000 ± 5120	14100000 ± 4990000	34900 ± 7860	103000000 ± 18700000
Cycle 1 Day 5 n=6,7,5,0,0,0,0	2230 ± 1110	3340 ± 2120	4390 ± 2270				
Cycle 2 Day 1 n=5,6,3,0,0,0,0	1720 ± 1020	2400 ± 1150	2870 ± 326				
Cycle 2 Day 5 n=3,5,3,0,0,0,0	1590 ± 577	2860 ± 1680	3030 ± 786				
Cycle 1 Day 15 n=0,0,0,9,0,0,0				15800 ± 11000			
Cycle 3 Day 1 n=0,0,0,0,5,2,3					20900000 ± 13000000	43500 ± 9110	166000000 ± 63600000

Area Under the Plasma Concentration Versus Time Curve From Time Zero to the Last Measurable Concentration Sampling Time (AUClast) for Ruxolitinib in Part 1

Description

Time Frame Days 1 and 5 of Cycles 1 and 2; Day 15 of Cycle 1

Analysis Population Description: The pharmacokinetic (PK) analysis set included all enrolled subjects who had an evaluable PK profile.

	Part 1: Ruxolitinib + Siremadlin 20 mg	Part 1: Ruxolitinib + Siremadlin 30 mg	Part 1: Ruxolitinib + Siremadlin 40 mg	Part 1: Ruxolitinib + Rineterkib 200 mg	Part 1: Ruxolitinib + Crizanlizumab	Part 1: Ruxolitinib + Sabatolimab	Part 1: Ruxolitinib + NIS793
Arm/Group Description	Dose escalation of siremadlin added to existing stable dose of ruxolitinib	Dose escalation of siremadlin added to existing stable dose of ruxolitinib	Dose escalation of siremadlin added to existing stable dose of ruxolitinib	Dose escalation of rineterkib added to existing stable dose of ruxolitinib	Safety run-in of crizanlizumab added to existing stable dose of ruxolitinib	Safety run-in of sabatolimab added to existing stable dose of ruxolitinib	Safety run-in of NIS793 added to existing stable dose of ruxolitinib
Number of Participants Analyzed [units: participants]	3	4	2	3	2	2	2
Area Under the Plasma Concentration Versus Time Curve From Time Zero to the Last Measurable Concentration Sampling Time (AUClast) for Ruxolitinib in Part 1 (units: ng*hr/mL)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
Ruxolitinib 5 mg Cycle 1 Day 1 n=0,0,2,1,0,0,0			344 ± 225	199 ± NA[1]			
Ruxolitinib 10 mg Cycle 1 Day 1 n=3,4,1,2,1,2,1	546 ± 412	673 ± 290	498 ± NA[1]	633 ± 393	440 ± NA[1]	336 ± 30.6	452 ± NA[1]
Ruxolitinib 15 mg Cycle 1 Day 1 n=1,0,2,1,2,0,2	1090 ± NA[1]		481 ± 243	729 ± NA[1]	662 ± 420		1220 ± 637
Ruxolitinib 20 mg Cycle 1 Day 1 n=3,2,1,3,1,0,0	991 ± 183	616 ± 107	623 ± NA[1]	913 ± 451	887 ± NA[1]		

Ruxolitinib 25 mg Cycle 1 Day 1 n=0,0,0,1,0,0,1				188 ± NA[1]	859 ± NA[1]
Ruxolitinib 5 mg Cycle 1 Day 5 n=0,0,2,0,0,0,0			245 ± 173		
Ruxolitinib 10 mg Cycle 1 Day 5 n=3,3,1,0,0,0,0,	465 ± 228	550 ± 307	441 ± NA[1]		
Ruxolitinib 15 mg Cycle 1 Day 5 n=1,1,2,0,0,0,0	849 ± NA[1]	901 ± NA[1]	454 ± 212		
Ruxolitinib 20 mg Cycle 1 Day 5 n=2,4,1,0,0,0,0	872 ± 218	652 ± 218	482 ± NA[1]		
Ruxolitinib 5 mg Cycle 1 Day 15 n=0,0,0,1,0,0,0				289 ± NA[1]	
Ruxolitinib 10 mg Cycle 1 Day 15 n=0,0,0,2,0,0,0				592 ± 403	
Ruxolitinib 15 mg Cycle 1 Day 15 n=0,0,0,1,0,0,0,				518 ± NA[1]	
Ruxolitinib 20 mg Cycle 1 Day 15 n=0,0,0,3,0,0,0				957 ± 479	
Ruxolitinib 25 mg Cycle 1 Day 15 n=0,0,0,1,0,0,0				718 ± NA[1]	
Ruxolitinib 5 mg Cycle 2 Day 1 n=0,0,1,0,0,0,0			172 ± NA[1]		
Ruxolitinib 10 mg Cycle 2 Day 1 n=2,2,1,0,0,0,0	354 ± 101	507 ± 225	553 ± NA[1]		
Ruxolitinib 15 mg Cycle 2 Day 1 n=1,2,2,0,0,0,0	1040 ± NA[1]	1190 ± 214	334 ± 98.7		
Ruxolitinib 20 mg Cycle 2 Day 1 n=3,3,1,0,0,0,0	823 ± 206	727 ± 200	521 ± NA[1]		

[1] Standard deviation was not calculable due to the single data point.

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Maximum (Peak) Observed Plasma Drug Concentration (Cmax) for Siremadlin, Rineterkib, Crizanlizumab, Sabatolimab, and NIS793 in Part 1

Description

Time Frame: Days 1 and 5 of Cycles 1 and 2 for siremadlin and Cycles 1 and 3 for crizanlizumab, sabatolimab, and NIS793; Days 1 and 15 of Cycle 1 for rineterkib

Analysis Population Description: The pharmacokinetic (PK) analysis set included all enrolled subjects who had an evaluable PK profile.

	Part 1: Ruxolitinib + Siremadlin 20 mg (Cmax for Siremadlin)	**Part 1: Ruxolitinib + Siremadlin 30 mg (Cmax for Siremadlin)**	**Part 1: Ruxolitinib + Siremadlin 40 mg (Cmax for Siremadlin)**	**Part 1: Ruxolitinib + Rineterkib 200 mg (Cmax for Rineterkib)**	**Part 1: Ruxolitinib + Crizanlizumab (Cmax for Crizanlizumab)**	**Part 1: Ruxolitinib + Sabatolimab (Cmax for Sabatolimab)**	**Part 1: Ruxolitinib + NIS793 (Cmax for NIS793)**
Arm/Group Description	Dose escalation of siremadlin added to existing stable dose of ruxolitinib	Dose escalation of siremadlin added to existing stable dose of ruxolitinib	Dose escalation of siremadlin added to existing stable dose of ruxolitinib	Dose escalation of rineterkib added to existing stable dose of ruxolitinib	Safety run-in of crizanlizumab added to existing stable dose of ruxolitinib	Safety run-in of sabatolimab added to existing stable dose of ruxolitinib	Safety run-in of NIS793 added to existing stable dose of ruxolitinib
Number of Participants Analyzed [units: participants]	6	9	5	9	5	2	4
Maximum (Peak) Observed Plasma Drug Concentration (Cmax) for Siremadlin, Rineterkib, Crizanlizumab, Sabatolimab, and NIS793 in Part 1 (units: ng/mL)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
Cycle 1 Day 1 n=6,9,5,9,5,2,4	118 ± 32.8	207 ± 122	290 ± 56.1	469 ± 358	114000 ± 36400	131 ± 17.7	439000 ± 56100

Cycle 1 Day 5 n=6,7,5,0,0,0,0	161 ± 78.0	284 ± 138	336 ± 109				
Cycle 2 Day 1 n=5,6,3,0,0,0,0	131 ± 57.9	142 ± 102	268 ± 15.0				
Cycle 2 Day 5 n=3,5,3,0,0,0,0	103 ± 34.1	193 ± 95.0	228 ± 58.3				
Cycle 1 Day 15 n=0,0,0,9,0,0,0				987 ± 621			
Cycle 3 Day 1 n=0,0,0,0,5,2,3					114000 ± 56600	150 ± 33.2	743000 ± 314000

Maximum (Peak) Observed Plasma Drug Concentration (Cmax) for Ruxolitinib in Part 1

Description

Time Frame: Days 1 and 5 of Cycles 1 and 2; Day 15 of Cycle 1

Analysis Population Description: The pharmacokinetic (PK) analysis set included all enrolled subjects who had an evaluable PK profile.

	Part 1: Ruxolitinib + Siremadlin 20 mg	**Part 1: Ruxolitinib + Siremadlin 30 mg**	**Part 1: Ruxolitinib + Siremadlin 40 mg**	**Part 1: Ruxolitinib + Rineterkib 200 mg**	**Part 1: Ruxolitinib + Crizanlizumab**	**Part 1: Ruxolitinib + Sabatolimab**	**Part 1: Ruxolitinib + NIS793**
Arm/Group Description	Dose escalation of siremadlin added to existing stable dose of ruxolitinib	Dose escalation of siremadlin added to existing stable dose of ruxolitinib	Dose escalation of siremadlin added to existing stable dose of ruxolitinib	Dose escalation of rineterkib added to existing stable dose of ruxolitinib	Safety run-in of crizanlizumab added to existing stable dose of ruxolitinib	Safety run-in of sabatolimab added to existing stable dose of ruxolitinib	Safety run-in of NIS793 added to existing stable dose of ruxolitinib
Number of Participants Analyzed [units: participants]	3	4	2	3	2	2	2

Maximum (Peak) Observed Plasma Drug Concentration (Cmax) for Ruxolitinib in Part 1 (units: ng/mL)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
Ruxolitinib 5 mg Cycle 1 Day 1 n=0,0,2,1,0,0,0			93.3 ± 26.5	67.4 ± NA[1]			
Ruxolitinib 10 mg Cycle 1 Day 1 n=3,4,1,2,1,2,1	184 ± 159	209 ± 20.8	108 ± NA[1]	195 ± 41.0	191 ± NA[1]	118 ± 33.0	132 ± NA[1]
Ruxolitinib 15 mg Cycle 1 Day 1 n=1,0,2,1,2,0,2	334 ± NA[1]		119 ± 76.2	193 ± NA[1]	185 ± 120		254 ± 73.5
Ruxolitinib 20 mg Cycle 1 Day 1 n=3,2,1,3,1,0,0	310 ± 131	184 ± 14.8	232 ± NA[1]	332 ± 33.5	221 ± NA[1]		
Ruxolitinib 25 mg Cycle 1 Day 1 n=0,0,0,1,0,0,1				46.0 ± NA[1]			224 ± NA[1]
Ruxolitinib 5 mg Cycle 1 Day 5 n=0,0,2,0,0,0,0			74.8 ± 13.5				
Ruxolitinib 10 mg Cycle 1 Day 5 n=3,3,1,0,0,0,0	152 ± 55.3	149 ± 67.6	107 ± NA[1]				
Ruxolitinib 15 mg Cycle 1 Day 5 n=1,1,2,0,0,0,0	252 ± NA[1]	264 ± NA[1]	172 ± 96.9				
Ruxolitinib 20 mg Cycle 1 Day 5 n=2,4,1,0,0,0,0	211 ± 48.8	232 ± 104	180 ± NA[1]				
Ruxolitinib 5 mg Cycle 1 Day 15 n=0,0,0,1,0,0,0				95.4 ± NA[1]			
Ruxolitinib 10 mg Cycle 1 Day 15 n=0,0,0,2,0,0,0				158 ± 68.6			
Ruxolitinib 15 mg Cycle 1 Day 15 n=0,0,0,1,0,0,0				126 ± NA[1]			
Ruxolitinib 20 mg Cycle 1 Day 15 n=0,0,0,3,0,0,0				369 ± 83.7			
Ruxolitinib 25 mg Cycle 1 Day 15 n=0,0,0,1,0,0,0				323 ± NA[1]			

Ruxolitinib 5 mg Cycle 2 Day 1 n=0,0,1,0,0,0,0			82.1 ± NA[1]
Ruxolitinib 10 mg Cycle 2 Day 1 n=2,2,1,0,0,0,0	119 ± 66.7	165 ± 29.7	90.5 ± NA[1]
Ruxolitinib 15 mg Cycle 2 Day 1 n=1,2,2,0,0,0,0	260 ± NA[1]	337 ± 70.7	100 ± 68.9
Ruxolitinib 20 mg Cycle 2 Day 1 n=3,3,1,0,0,0,0	257 ± 71.0	176 ± 66.0	241 ± NA[1]

[1] Standard deviation was not calculable due to the single data point.

Time to Reach Maximum (Peak) Plasma, Blood, Serum or Other Body Fluid Drug Concentration After Single Dose Administration (Tmax) for Siremadlin, Rineterkib, Crizanlizumab, Sabatolimab, and NIS793 in Part 1

Description

Time Frame: Days 1 and 5 of Cycles 1 and 2 for siremadlin and Cycles 1 and 3 for crizanlizumab, sabatolimab, and NIS793; Days 1 and 15 of Cycle 1 for rineterkib

Analysis Population Description: The pharmacokinetic (PK) analysis set included all enrolled subjects who had an evaluable PK profile.

	Part 1: Ruxolitinib + Siremadlin 20 mg (Tmax for Siremadlin)	**Part 1: Ruxolitinib + Siremadlin 30 mg (Tmax for Siremadlin)**	**Part 1: Ruxolitinib + Siremadlin 40 mg (Tmax for Siremadlin)**	**Part 1: Ruxolitinib + Rineterkib 200 mg (Tmax for Rineterkib)**	**Part 1: Ruxolitinib + Crizanlizumab (Tmax for Crizanlizumab)**	**Part 1: Ruxolitinib + Sabatolimab (Tmax for Sabatolimab)**	**Part 1: Ruxolitinib + NIS793 (Tmax for NIS793)**
Arm/Group Description	Dose escalation of siremadlin added to existing stable dose of ruxolitinib	Dose escalation of siremadlin added to existing stable dose of ruxolitinib	Dose escalation of siremadlin added to existing stable dose of ruxolitinib	Dose escalation of rineterkib added to existing stable dose of ruxolitinib	Safety run-in of crizanlizumab added to existing stable dose of ruxolitinib	Safety run-in of sabatolimab added to existing stable dose of ruxolitinib	Safety run-in of NIS793 added to existing stable dose of ruxolitinib

Number of Participants Analyzed [units: participants]	6	9	5	9	5	2	4
Time to Reach Maximum (Peak) Plasma, Blood, Serum or Other Body Fluid Drug Concentration After Single Dose Administration (Tmax) for Siremadlin, Rineterkib, Crizanlizumab, Sabatolimab, and NIS793 in Part 1 (units: hours)	**Median (Full Range)**	**Median (Full Range)**	**Median (Full Range)**	**Median (Full Range)**	**Median (Full Range)**	**Median (Full Range)**	**Median (Full Range)**
Cycle 1 Day 1 n=6,9,5,9,5,2,4	2.52 (1.83 to 23.5)	3.00 (1.92 to 7.45)	3.93 (2.00 to 8.00)	3.92 (1.98 to 24.0)	1.82 (1.50 to 2.27)	1.84 (1.67 to 2.00)	2.00 (1.95 to 2.98)
Cycle 1 Day 5 n=6,7,5,0,0,0,0	3.44 (1.83 to 4.07)	2.90 (2.00 to 3.97)	2.87 (1.88 to 3.03)				
Cycle 2 Day 1 n=5,6,3,0,0,0,0	1.95 (0.980 to 4.10)	3.92 (2.83 to 23.9)	2.88 (2.08 to 7.07)				
Cycle 2 Day 5 n=3,5,3,0,0,0,0	3.00 (2.95 to 3.17)	2.93 (2.75 to 3.17)	3.02 (2.92 to 3.08)				
Cycle 1 Day 15 n=0,0,0,9,0,0,0				2.50 (0.500 to 4.00)			
Cycle 3 Day 1 n=0,0,0,0,5,2,3					1.65 (0.750 to 2.13)	2.01 (1.85 to 2.17)	1.97 (1.92 to 2.33)

Time to Reach Maximum (Peak) Plasma, Blood, Serum or Other Body Fluid Drug Concentration After Single Dose Administration (Tmax) for Ruxolitinib in Part 1

Description

Time Frame Days 1 and 5 of Cycles 1 and 2; Day 15 of Cycle 1

Analysis Population Description: The pharmacokinetic (PK) analysis set included all enrolled subjects who had an evaluable PK profile.

	Part 1: Ruxolitinib + Siremadlin 20 mg	Part 1: Ruxolitinib + Siremadlin 30 mg	Part 1: Ruxolitinib + Siremadlin 40 mg	Part 1: Ruxolitinib + Rineterkib 200 mg	Part 1: Ruxolitinib + Crizanlizumab	Part 1: Ruxolitinib + Sabatolimab	Part 1: Ruxolitinib + NIS793
Arm/Group Description	Dose escalation of siremadlin added to existing stable dose of ruxolitinib	Dose escalation of siremadlin added to existing stable dose of ruxolitinib	Dose escalation of siremadlin added to existing stable dose of ruxolitinib	Dose escalation of rineterkib added to existing stable dose of ruxolitinib	Safety run-in of crizanlizumab added to existing stable dose of ruxolitinib	Safety run-in of sabatolimab added to existing stable dose of ruxolitinib	Safety run-in of NIS793 added to existing stable dose of ruxolitinib
Number of Participants Analyzed [units: participants]	3	4	2	3	2	2	2
Time to Reach Maximum (Peak) Plasma, Blood, Serum or Other Body Fluid Drug Concentration After Single Dose Administration (Tmax) for Ruxolitinib in Part 1 (units: hours)	**Median (Full Range)**	**Median (Full Range)**	**Median (Full Range)**	**Median (Full Range)**	**Median (Full Range)**	**Median (Full Range)**	**Median (Full Range)**
Ruxolitinib 5 mg Cycle 1 Day 1 n=0,0,2,1,0,0,0			0.960 (0.920 to 1.00)	0.500 (0.500 to 0.500)			
Ruxolitinib 10 mg Cycle 1 Day 1 n=3,4,1,2,1,2,1	0.550 (0.330 to 6.18)	0.775 (0.500 to 1.08)	0.500 (0.500 to 0.500)	0.485 (0.470 to 0.500)	0.580 (0.580 to 0.580)	0.460 (0.00 to 0.920)	1.67 (1.67 to 1.67)
Ruxolitinib 15 mg Cycle 1 Day 1 n=1,0,2,1,2,0,2	0.650 (0.650 to 0.650)		1.96 (1.92 to 2.00)	0.420 (0.420 to 0.420)	1.80 (1.75 to 1.85)		2.42 (1.08 to 3.75)

Ruxolitinib 20 mg Cycle 1 Day 1 n=3,2,1,3,1,0,0	0.530 (0.500 to 1.00)	1.54 (1.08 to 2.00)	1.00 (1.00 to 1.00)	0.450 (0.420 to 1.03)	1.17 (1.17 to 1.17)		
Ruxolitinib 25 mg Cycle 1 Day 1 n=0,0,0,1,0,0,1				0.00 (0.00 to 0.00)			2.00 (2.00 to 2.00)
Ruxolitinib 5 mg Cycle 1 Day 5 n=0,0,2,0,0,0,0			0.960 (0.920 to 1.00)				
Ruxolitinib 10 mg Cycle 1 Day 5 n=3,3,1,0,0,0,0	1.00 (0.830 to 2.02)	0.980 (0.920 to 2.03)	1.00 (1.00 to 1.00)				
Ruxolitinib 15 mg Cycle 1 Day 5 n=1,1,2,0,0,0,0	0.970 (0.970 to 0.970)	0.830 (0.830 to 0.830)	0.955 (0.830 to 1.08)				
Ruxolitinib 20 mg Cycle 1 Day 5 n=2,4,1,0,0,0,0	0.925 (0.850 to 1.00)	1.00 (0.920 to 1.08)	0.830 (0.830 to 0.830)				
Ruxolitinib 5 mg Cycle 1 Day 15 n=0,0,0,1,0,0,0				0.500 (0.500 to 0.500)			
Ruxolitinib 10 mg Cycle 1 Day 15 n=0,0,0,2,0,0,0				1.98 (1.95 to 2.00)			
Ruxolitinib 15 mg Cycle 1 Day 15 n=0,0,0,1,0,0,0				0.500 (0.500 to 0.500)			
Ruxolitinib 20 mg Cycle 1 Day 15 n=0,0,0,3,0,0,0				0.650 (0.500 to 1.00)			
Ruxolitinib 25 mg Cycle 1 Day 15 n=0,0,0,1,0,0,0				0.500 (0.500 to 0.500)			
Ruxolitinib 5 mg Cycle 2 Day 1 n=0,0,1,0,0,0,0			0.900 (0.900 to 0.900)				
Ruxolitinib 10 mg Cycle 2 Day 1 n=2,2,1,0,0,0,0	0.895 (0.870 to 0.920)	1.00 (0.920 to 1.08)	2.00 (2.00 to 2.00)				

Ruxolitinib 15 mg Cycle 2 Day 1 n=1,2,2,0,0,0,0	1.05 (1.05 to 1.05)	1.46 (1.00 to 1.92)	4.00 (0.920 to 7.07)
Ruxolitinib 20 mg Cycle 2 Day 1 n=3,3,1,0,0,0,0	0.980 (0.880 to 1.02)	1.02 (1.00 to 4.00)	0.930 (0.930 to 0.930)

Concentration Versus Time Profile for Siremadlin in Part 1

Description

Time Frame: Day 1 of Cycles 1 and 2; Day 6 of Cycle 1; Days 2 and 5 of Cycles 1, 2, 3, 4, 5, and 6. Each cycle was 28 days.

Analysis Population Description: The pharmacokinetic (PK) analysis set included all enrolled subjects who had an evaluable PK profile.

	Part 1: Ruxolitinib + Siremadlin 20 mg	**Part 1: Ruxolitinib + Siremadlin 30 mg**	**Part 1: Ruxolitinib + Siremadlin 40 mg**
Arm/Group Description	Dose escalation of siremadlin added to existing stable dose of ruxolitinib	Dose escalation of siremadlin added to existing stable dose of ruxolitinib	Dose escalation of siremadlin added to existing stable dose of ruxolitinib
Number of Participants Analyzed [units: participants]	7	10	5
Concentration Versus Time Profile for Siremadlin in Part 1 (units: ng/mL)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
Cycle 1 Day 1, 0 hr (pre-dose) n=6,7,5	0 ± 0	0 ± 0	0 ± 0
Cycle 1 Day 1, 0.5 hr n=6,8,5	7.46 ± 6.23	4.76 ± 8.02	12.8 ± 21.0
Cycle 1 Day 1, 1 hr n=6,9,5	52.7 ± 27.0	38.8 ± 40.9	87.0 ± 73.6
Cycle 1 Day 1, 2 hr n=6,9,5	104 ± 53.3	146 ± 95.1	199 ± 139
Cycle 1 Day 1, 3 hr n=6,9,4	102 ± 51.8	178 ± 96.3	192 ± 137
Cycle 1 Day 1, 4 hr n=6,9,5	92.9 ± 44.0	181 ± 116	201 ± 109

Cycle 1 Day 1, 8 hr n=6,9,5	75.7 ± 36.9	146 ± 77.0	212 ± 55.5
Cycle 1 Day 2, 24 hr n=6,10,4	42.0 ± 23.7	59.7 ± 49.4	95.3 ± 41.2
Cycle 1 Day 5, 0 hr (pre-dose) n=6,7,5	43.5 ± 42.2	88.4 ± 73.6	77.6 ± 84.2
Cycle 1 Day 5,1 hr n=6,6,5	72.9 ± 28.3	171 ± 89.8	155 ± 123
Cycle 1 Day 5, 2 hr n=6,7,5	127 ± 63.7	260 ± 128	324 ± 112
Cycle 1 Day 5, 3 hr n=6,7,5	144 ± 74.6	260 ± 130	333 ± 108
Cycle 1 Day 5, 4 hr n=5,7,5	133 ± 67.4	226 ± 111	295 ± 97.9
Cycle 1 Day 5, 8 hr n=7,8,3	110 ± 54.3	160 ± 83.1	247 ± 126
Cycle 1 Day 6, 24 hr n=7,8,5	45.4 ± 35.9	75.1 ± 66.5	72.2 ± 90.5
Cycle 2 Day 1, 0 hr (pre-dose) n=4,5,3	0 ± 0	0 ± 0	0 ± 0
Cycle 2 Day 1, 1 hr n=5,5,3	71.8 ± 92.9	25.5 ± 28.4	32.2 ± 28.7
Cycle 2 Day 1, 2 hr n=5,5,2	116 ± 64.7	100 ± 64.8	144 ± 200
Cycle 2 Day 1, 3 hr n=5,5,3	111 ± 58.2	146 ± 99.5	178 ± 147
Cycle 2 Day 1, 4 hr n=5,5,3	114 ± 52.8	158 ± 78.4	164 ± 102
Cycle 2 Day 1, 8 hr n=4,5,3	90.9 ± 39.1	122 ± 54.5	189 ± 63.2
Cycle 2 Day 2, 24 hr n=4,5,3	67.3 ± 49.3	48.5 ± 44.2	31.7 ± 5.42
Cycle 2 Day 5, 0 hr (pre-dose) n=4,7,3	24.3 ± 23.8	42.5 ± 50.8	29.2 ± 6.67
Cycle 2 Day 5, 3 hr n=3,6,3	103 ± 34.1	181 ± 89.7	228 ± 58.3
Cycle 2 Day 6, 24 hr n=4,5,3	34.7 ± 13.2	51.5 ± 58.3	27.5 ± 6.45
Cycle 3 Day 2, 0 hr (pre-dose) n=3,4,4	43.5 ± 16.5	79.1 ± 96.9	39.2 ± 20.5
Cycle 3 Day 5, 0 hr (pre-dose) n=5,6,3	56.8 ± 47.9	81.0 ± 73.9	29.7 ± 23.3
Cycle 4 Day 2, 0 hr (pre-dose) n=5,5,1	36.3 ± 21.7	63.0 ± 52.4	10.9 ± NA[1]
Cycle 4 Day 5, 0 hr (pre-dose) n=5,6,1	40.4 ± 29.7	50.1 ± 48.1	10.5 ± NA[1]
Cycle 5 Day 2, 0 hr (pre-dose) n=6,4,4	40.0 ± 29.3	146 ± 180	49.2 ± 25.1
Cycle 5 Day 5, 0 hr (pre-dose) n=6,4,3	78.3 ± 90.2	124 ± 129	32.5 ± 13.5
Cycle 6 Day 2, 0 hr (pre-dose) n=5,2,1	48.0 ± 28.2	60.2 ± 37.0	16.4 ± NA[1]

Cycle 6 Day 5, 0 hr (pre-dose) n=4,2,1	79.0 ± 52.2	68.9 ± 68.1	9.02 ± NA[1]

[1] Standard deviation was not calculable due to the single data point.

Concentration Versus Time Profile for Rineterkib in Part 1

Description

Time Frame: Days 1, 2, 15, and 16 of Cycle 1; Day 1 of Cycles 2, 3, 4, 5, and 6. Each cycle was 28 days.

Analysis Population Description: The pharmacokinetic (PK) analysis set included all enrolled subjects who had an evaluable PK profile.

	Part 1: Ruxolitinib + Rineterkib 200 mg
Arm/Group Description	Dose escalation of rineterkib added to existing stable dose of ruxolitinib
Number of Participants Analyzed [units: participants]	9
Concentration Versus Time Profile for Rineterkib in Part 1 (units: ng/mL)	**Mean ± Standard Deviation**
Cycle 1 Day 1, 0 hr (pre-dose) n=9	0 ± 0
Cycle 1 Day 1, 0.5 hr n=9	68.3 ± 68.8
Cycle 1 Day 1, 1 hr n=8	235 ± 343
Cycle 1 Day 1, 2 hr n=8	340 ± 229
Cycle 1 Day 1, 3 hr n=9	352 ± 244
Cycle 1 Day 1, 4 hr n=9	325 ± 173
Cycle 1 Day 1, 8 hr n=7	244 ± 128
Cycle 1 Day 2, 24 hr n=9	261 ± 419
Cycle 1 Day 2, 0 hr (pre-dose) n=8	234 ± 440
Cycle 1 Day 15, 0 hr (pre-dose) n=8	330 ± 222
Cycle 1 Day 15 0.5 hr n=8	581 ± 464

Cycle 1 Day 15, 1 hr n=n=9	735 ± 620
Cycle 1 Day 15, 2 hr n=8	749 ± 512
Cycle 1 Day 15, 3 hr n=8	789 ± 616
Cycle 1 Day 15, 4 hr n=8	771 ± 484
Cycle 1 Day 15, 8 hr n=9	633 ± 403
Cycle 1 Day 16, 24 hr n=8	528 ± 618
Cycle 1 Day 16, 0 hr (pre-dose) n=8	305 ± 222
Cycle 2 Day 1, 0 hr (pre-dose) n=9	314 ± 171
Cycle 3 Day 1, 0 hr (pre-dose) n=6	406 ± 341
Cycle 4 Day 1, 0 hr (pre-dose) n=5	402 ± 364
Cycle 5 Day 1, 0 hr (pre-dose) n=3	232 ± 165
Cycle 6 Day 1, 0 hr (pre-dose) n=3	340 ± 125

Concentration Versus Time Profile for Crizanlizumab in Part 1

Description	EOI = end of infusion
Time Frame	Days 1, 2, 8, and 15 of Cycles 1, 2, and 3; Day 1 of Cycles 4, 5, 6, and 9. Each cycle was 28 days.
Analysis Population Description	The pharmacokinetic (PK) analysis set included all enrolled subjects who had an evaluable PK profile.

	Part 1: Ruxolitinib + Crizanlizumab
Arm/Group Description	Safety run-in of crizanlizumab added to existing stable dose of ruxolitinib
Number of Participants Analyzed [units: participants]	5
Concentration Versus Time Profile for Crizanlizumab in Part 1 (units: ng/mL)	**Mean ± Standard Deviation**

Cycle 1 Day 1, 0 H / PRE-INFUSION n=4	0 ± 0
Cycle 1 Day 1, 1H POST EOI n=5	114000 ± 36400
Cycle 1 Day 2, 24H POST START OF INFUSION n=4	78700 ± 10500
Cycle 1 Day 8, 168H POST START OF INFUSION n=5	28700 ± 12200
Cycle 1 Day 15, 336H POST START OF INFUSION n=5	9280 ± 4540
Cycle 1 Day 15, 0 H / PRE-INFUSION n=1	7710 ± NA[1]
Cycle 2 Day 1, 0 H / PRE-INFUSION n=5	20700 ± 8980
Cycle 2 Day 1, 1H POST EOI n=5	135000 ± 43100
Cycle 2 Day 1, 336H POST START OF INFUSION n=1,	15500 ± NA[1]
Cycle 3 Day 1, 672H POST START OF INFUSION n=5	8710 ± 8350
Cycle 3 Day 1, 0 H / PRE-INFUSION n=5	8710 ± 8350
Cycle 3 Day 1, 1H POST EOI n=4	103000 ± 59200
Cycle 3 Day 2, 24H POST START OF INFUSION n=5	95500 ± 42300
Cycle 3 Day 8, 168H POST START OF INFUSION n=5	37100 ± 19400
Cycle 3 Day 15, 336H POST START OF INFUSION n=5	21000 ± 17700
Cycle 4 Day 1, 672H POST START OF INFUSION n=5	5900 ± 6710
Cycle 4 Day 1, 0 H / PRE-INFUSION n=5	5900 ± 6710
Cycle 4 Day 1, 1H POST EOI n=5	128000 ± 33200
Cycle 5 Day 1, 672H POST START OF INFUSION n=4	6780 ± 7830
Cycle 5 Day 1, 0 H / PRE-INFUSION n=4	6780 ± 7830
Cycle 5 Day 1, 1H POST EOI n=3	122000 ± 29400
Cycle 6 Day 1, 672H POST START OF INFUSION n=4	6930 ± 8000
Cycle 6 Day 1, 0 H / PRE-INFUSION n=4	6930 ± 8000
Cycle 6 Day 1, 1H POST EOI n=4	128000 ± 39600
Cycle 9 Day 1, 0 H / PRE-INFUSION n=3	5500 ± 9530

[1] Standard deviation was not calculable due to the single data point.

Concentration Versus Time Profile for Sabatolimab in Part 1

Description	EOI = end of infusion
Time Frame	Days 1, 2, 8, and 15 of Cycles 1, 2, and 3; Day 1 of Cycles 4 and 5. Each cycle was 28 days.
Analysis Population Description	The pharmacokinetic (PK) analysis set included all enrolled subjects who had an evaluable PK profile.

	Part 1: Ruxolitinib + Sabatolimab
Arm/Group Description	Safety run-in of sabatolimab added to existing stable dose of ruxolitinib
Number of Participants Analyzed [units: participants]	2
Concentration Versus Time Profile for Sabatolimab in Part 1 (units: ng/mL)	**Mean ± Standard Deviation**
Cycle 1 Day 1, 0 H / PRE-INFUSION n=2	0 ± 0
Cycle 1 Day 1, 1H POST EOI n=1	143 ± NA[1]
Cycle 1 Day 2, 24H POST START OF INFUSION n=2	109 ± 13.2
Cycle 1 Day 8, 168H POST START OF INFUSION n=1	57.0 ± NA[1]
Cycle 1 Day 15, 336H POST START OF INFUSION n=2	41.8 ± 7.28
Cycle 2 Day 1, 672H POST START OF INFUSION n=2	16.1 ± 9.16
Cycle 2 Day 1, 0 H / PRE-INFUSION n=2	16.1 ± 9.16
Cycle 2 Day 1, 1H POST EOI n=1	126 ± NA[1]
Cycle 3 Day 1, 672H POST START OF INFUSION n=2	26.0 ± 5.09
Cycle 3 Day 1, 0 H / PRE-INFUSION n=2	26.0 ± 5.09
Cycle 3 Day 1, 1H POST EOI n=2	150 ± 33.2
Cycle 3 Day 2, 24H POST START OF INFUSION n=2	125 ± 10.6

Cycle 3 Day 8, 168H POST START OF INFUSION n=2	80.5 ± 19.1
Cycle 3 Day 15, 336H POST START OF INFUSION n=2	58.0 ± 12.3
Cycle 4 Day 1, 672H POST START OF INFUSION n=1	31.1 ± NA[1]
Cycle 4 Day 1, 0 H / PRE-INFUSION n=2	30.0 ± 1.56
Cycle 4 Day 1, 1H POST EOI n=2	141 ± 11.3
Cycle 5 Day 1, 0 H / PRE-INFUSION n=2	32.9 ± 3.82
Cycle 5 Day 1, 1H POST EOI n=2	152 ± 9.19

[1] Standard deviation was not calculable due to the single data point.

Concentration Versus Time Profile for NIS793 in Part 1

Description	EOI = end of infusion
Time Frame	Days 1, 2, 4, 8, 11, and 15 of Cycles 1, 2, and 3; Day 1 of Cycles 4 and 5. Each cycle was 28 days.
Analysis Population Description	The pharmacokinetic (PK) analysis set included all enrolled subjects who had an evaluable PK profile.

	Part 1: Ruxolitinib + NIS793
Arm/Group Description	Safety run-in of NIS793 added to existing stable dose of ruxolitinib
Number of Participants Analyzed [units: participants]	4
Concentration Versus Time Profile for NIS793 in Part 1 (units: ng/mL)	**Mean ± Standard Deviation**
Cycle 1 Day 1, 0 H / PRE-INFUSION n=4	0 ± 0
Cycle 1 Day 1, 1H POST EOI n=4	439000 ± 56100
Cycle 1 Day 2, 24H POST START OF INFUSION n=4	349000 ± 52800
Cycle 1 Day 4, 72H POST START OF INFUSION n=4	279000 ± 48400
Cycle 1 Day 8, 168H POST START OF INFUSION n=3	196000 ± 31000

Cycle 1 Day 11, 240H POST START OF INFUSION n=4	183000 ± 45400
Cycle 1 Day 15, 336H POST START OF INFUSION n=4	161000 ± 37500
Cycle 2 Day 1, 504H POST START OF INFUSION n=4	132000 ± 33300
Cycle 2 Day 1, 0 H / PRE-INFUSION n=4	132000 ± 33300
Cycle 3 Day 1, 0 H / PRE-INFUSION n=3	187000 ± 61000
Cycle 3 Day 1, 1H POST EOI n=3	743000 ± 314000
Cycle 3 Day 2, 24H POST START OF INFUSION n=2	632000 ± 17000
Cycle 3 Day 4, 72H POST START OF INFUSION n=3	448000 ± 114000
Cycle 3 Day 8, 168H POST START OF INFUSION n=3	383000 ± 103000
Cycle 3 Day 11, 240H POST START OF INFUSION n=2	262000 ± 93300
Cycle 3 Day 15, 336H POST START OF INFUSION n=3	265000 ± 51500
Cycle 4 Day 1, 504H POST START OF INFUSION n=1	281000 ± NA[1]
Cycle 4 Day 1, 0 H / PRE-INFUSION n=2	232000 ± 70000
Cycle 5 Day 1, 0 H / PRE-INFUSION n=1	280000 ± NA[1]

[1] Standard deviation was not calculable due to the single data point.

Concentration Versus Time Profile for Ruxolitinib in Part 1

Description

Time Frame: Days 1, 2, 5, 6, and 15 of Cycles 1 and 2; Day 16 of Cycle 1; Days 1, 2, and 15 of Cycle 3; Days 1 and 5 of Cycles 4, 5, and 6. Each cycle was 28 days.

Analysis Population Description: The pharmacokinetic (PK) analysis set included all enrolled subjects who had an evaluable PK profile.

	Part 1: Ruxolitinib + Siremadlin 20 mg	**Part 1: Ruxolitinib + Siremadlin 30 mg**	**Part 1: Ruxolitinib + Siremadlin 40 mg**	**Part 1: Ruxolitinib + Rineterkib 200 mg**	**Part 1: Ruxolitinib + Crizanlizumab**	**Part 1: Ruxolitinib + Sabatolimab**	**Part 1: Ruxolitinib + NIS793**

Arm/Group Description	Dose escalation of siremadlin added to existing stable dose of ruxolitinib	Dose escalation of siremadlin added to existing stable dose of ruxolitinib	Dose escalation of siremadlin added to existing stable dose of ruxolitinib	Dose escalation of rineterkib added to existing stable dose of ruxolitinib	Safety run-in of crizanlizumab added to existing stable dose of ruxolitinib	Safety run-in of sabatolimab added to existing stable dose of ruxolitinib	Safety run-in of NIS793 added to existing stable dose of ruxolitinib
Number of Participants Analyzed [units: participants]	7	8	6	8	4	2	4
Concentration Versus Time Profile for Ruxolitinib in Part 1 (units: ng/mL)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
Cycle 1 Day 1, 0 hr (pre-dose) n=6,6,5,7,3,2,4	34.7 ± 17.8	21.3 ± 14.5	11.8 ± 13.4	20.1 ± 16.1	12.9 ± 6.31	51.2 ± 61.0	37.9 ± 48.4
Cycle 1 Day 1, 0.5 hr n=6,5,6,8,2,2,3	284 ± 128	152 ± 91.1	95.7 ± 63.2	185 ± 100	107 ± 119	57.1 ± 44.0	108 ± 128
Cycle 1 Day 1, 1 hr n=6,6,6,7,2,2,3	240 ± 78.9	167 ± 51.7	124 ± 64.5	192 ± 106	65.7 ± 59.9	110 ± 44.1	164 ± 140
Cycle 1 Day 1, 2 hr n=6,6,6,7,2,2,3	174 ± 55.3	143 ± 48.6	98.9 ± 46.2	140 ± 112	170 ± 140	72.7 ± 4.10	187 ± 105
Cycle 1 Day 1, 3 hr n=6,6,5,8,2,2,3	125 ± 36.6	114 ± 42.1	62.4 ± 31.1	97.4 ± 75.7	124 ± 91.0	54.4 ± 10.4	184 ± 77.9
Cycle 1 Day 1, 4 hr n=6,6,6,8,2,2,3	93.2 ± 26.5	77.8 ± 40.0	50.2 ± 23.4	59.2 ± 46.1	101 ± 81.2	28.3 ± 7.28	190 ± 58.4
Cycle 1 Day 1, 8 hr n=6,6,6,8,4,2,3	51.6 ± 18.7	32.2 ± 19.1	24.0 ± 15.0	29.9 ± 19.8	39.5 ± 29.2	7.75 ± 1.52	44.4 ± 35.3
Cycle 1 Day 2, 0 hr (pre-dose) n=7,6,4,8,1,1,0	18.2 ± 13.0	13.4 ± 11.1	11.2 ± 16.2	17.6 ± 19.9	30.3 ± NA[1]	0 ± NA[1]	
Cycle 1 Day 5, 0 hr (pre-dose) n=6,8,6,0,0,0,0	15.5 ± 13.9	14.7 ± 14.0	9.33 ± 10.6				
Cycle 1 Day 5, 1 hr n=6,7,6,0,0,0,0	160 ± 79.5	221 ± 83.7	130 ± 66.6				

Cycle 1 Day 5, 2 hr n=6,8,6,0,0,0,0	149 ± 64.0	140 ± 45.6	90.0 ± 41.4				
Cycle 1 Day 5, 3 hr n=6,8,6,0,0,0,0	104 ± 45.2	100 ± 39.1	61.8 ± 31.7				
Cycle 1 Day 5, 4 hr n=6,8,6,0,0,0,0	81.4 ± 38.4	71.2 ± 30.1	34.1 ± 16.1				
Cycle 1 Day 5, 8 hr n=6,8,4,0,0,0,0	37.6 ± 22.6	22.9 ± 13.7	16.2 ± 13.4				
Cycle 1 Day 6, 0 hr (pre-dose) n=6,7,5,0,0,0,0	11.5 ± 12.1	37.8 ± 63.4	6.28 ± 9.31				
Cycle 1 Day 15, 0 hr (pre-dose) n=7,8,4,7,3,2,0	23.2 ± 34.0	23.6 ± 19.8	11.2 ± 17.4	11.9 ± 14.2	12.6 ± 10.1	4.06 ± 2.28	
Cycle 1 Day 15, 0.5 hr n=0,0,0,7,0,0,0				231 ± 115			
Cycle 1 Day 15, 1 hr n=0,0,0,8,0,0,0				194 ± 139			
Cycle 1 Day 15, 2 hr n=0,0,0,7,0,0,0				126 ± 58.7			
Cycle 1 Day 15, 3 hr n=0,0,0,7,0,0,0				103 ± 59.6			
Cycle 1 Day 15, 4 hr n=0,0,0,7,0,0,0				76.3 ± 53.5			
Cycle 1 Day 15, 8 hr n=0,0,0,8,0,0,0				27.9 ± 21.7			
Cycle 1 Day 16, 0 hr (pre-dose) n=0,0,0,6,0,0,0				14.4 ± 15.2			
Cycle 2 Day 1, 0 hr (pre-dose) n=6,7,5,8,4,2,3	25.9 ± 23.4	19.3 ± 18.8	11.4 ± 20.7	45.7 ± 108	13.7 ± 4.84	28.4 ± 39.1	65.1 ± 88.9
Cycle 2 Day 1, 1 hr n=6,7,5,0,0,0,0	212 ± 89.8	186 ± 113	114 ± 82.4				
Cycle 2 Day 1, 2 hr n=6,7,4,0,0,0,0	144 ± 76.0	165 ± 82.2	56.2 ± 30.9				

Cycle 2 Day 1, 3 hr n=6,7,5,0,0,0,0	108 ± 50.8	127 ± 61.7	50.3 ± 26.4				
Cycle 2 Day 1, 4 hr n=5,7,5,0,0,0,0	89.9 ± 39.8	106 ± 39.5	45.6 ± 25.8				
Cycle 2 Day 1, 8 hr n=4,6,5,0,0,0,0	47.3 ± 31.5	45.8 ± 19.4	30.9 ± 28.1				
Cycle 2 Day 2, 0 hr (pre-dose) n=3,6,5,0,0,0,0	74.0 ± 62.3	19.2 ± 19.7	13.9 ± 20.5				
Cycle 2 Day 5, 0 hr (pre-dose) n=3,8,4,0,0,0,0	15.4 ± 6.29	15.2 ± 11.3	4.45 ± 4.57				
Cycle 2 Day 6, 0 hr (pre-dose) n=4,5,4,0,0,0,0	7.36 ± 7.32	46.8 ± 80.0	2.40 ± 2.74				
Cycle 2 Day 15, 0 hr (pre-dose) n=6,8,3,0,1,2,0	22.4 ± 17.2	22.1 ± 22.7	1.93 ± 1.65		63.6 ± NA[1]	7.95 ± 8.14	
Cycle 3 Day 1, 0 hr (pre-dose) n=7,7,4,6,4,2,2	24.2 ± 15.5	23.2 ± 21.8	4.50 ± 4.03	11.1 ± 10.9	12.0 ± 6.36	2.44 ± 1.46	84.6 ± 96.8
Cycle 3 Day 2, 0 hr (pre-dose) n=5,6,3,0,0,0,0	12.6 ± 13.9	31.9 ± 38.9	2.33 ± 1.57				
Cycle 3 Day 15, 0 hr (pre-dose) n=5,5,2,0,4,2,0	18.7 ± 18.4	45.2 ± 41.5	3.95 ± 4.10		10.9 ± 6.89	12.5 ± 9.14	
Cycle 4 Day 1, 0 hr (pre-dose) n=7,5,3,5,4,1,1	17.5 ± 18.2	20.9 ± 22.2	4.53 ± 6.44	18.2 ± 33.8	14.0 ± 7.81	2.94 ± NA[1]	24.4 ± NA[1]
Cycle 4 Day 5, 0 hr (pre-dose) n=5,6,3,0,0,0,0	13.6 ± 13.7	9.12 ± 13.5	7.99 ± 11.4				
Cycle 5 Day 1, 0 hr (pre-dose) n=7,6,4,3,3,0,0	16.4 ± 16.1	12.7 ± 12.0	5.30 ± 5.94	10.3 ± 13.6	20.1 ± 23.0		
Cycle 5 Day 5, 0 hr (pre-dose) n=5,3,3,0,0,0,0	26.6 ± 16.4	9.54 ± 13.2	2.79 ± 2.46				
Cycle 6 Day 1, 0 hr (pre-dose) n=4,4,2,3,3,0,0	15.8 ± 19.5	17.0 ± 19.7	0.608 ± 0.0672	21.9 ± 23.2	27.3 ± 32.8		
Cycle 6 Day 5, 0 hr (pre-dose) n=3,4,2,0,0,0,0	24.8 ± 19.9	11.5 ± 8.34	0.957 ± 0.528				

[1] Standard deviation was not calculable due to the single data point.

Other Pre-Specified Outcome Result(s)

No data identified.

Post-Hoc Outcome Result(s)

No data identified.

Safety Results

Time Frame	Adverse events were reported from first dose of study treatment until end of study treatment plus post-treatment safety follow-up, up to a maximum duration of approximately 44 months.
Source Vocabulary for Table Default	MedDRA (27.0)
Collection Approach for Table Default	Systematic Assessment

All-Cause Mortality

	Part 1: Ruxolitinib + Siremadlin 20 mg N = 7	Part 1: Ruxolitinib + Siremadlin 30 mg N = 10	Part 1: Ruxolitinib + Siremadlin 40 mg N = 6	Part 1: Ruxolitinib + Siremadlin Total N = 23	Part 1: Ruxolitinib + Rineterkib 200 mg N = 9	Part 1: Ruxolitinib + Crizanlizumab N = 6	Part 1: Ruxolitinib + Sabatolimab N = 2	Part 1: Ruxolitinib + NIS793 N = 4	Part 2: Ruxolitinib N = 1	All Subjects N = 45

Arm/Group Description	Dose escalation of siremadlin added to existing stable dose of ruxolitinib	Dose escalation of siremadlin added to existing stable dose of ruxolitinib	Dose escalation of siremadlin added to existing stable dose of ruxolitinib	Total	Dose escalation of rineterkib added to existing stable dose of ruxolitinib	Safety run-in of crizanlizumab added to existing stable dose of ruxolitinib	Safety run-in of sabatolimab added to existing stable dose of ruxolitinib	Safety run-in of NIS793 added to existing stable dose of ruxolitinib	Existing stable dose of ruxolitinib as control for Part 2	All Subjects
Total Number Affected	0	0	3	3	1	0	0	0	0	4
Total Number At Risk	7	10	6	23	9	6	2	4	1	45

Serious Adverse Events

Time Frame	Adverse events were reported from first dose of study treatment until end of study treatment plus post-treatment safety follow-up, up to a maximum duration of approximately 44 months.
Source Vocabulary for Table Default	MedDRA (27.0)
Collection Approach for Table Default	Systematic Assessment

	Part 1: Ruxolitinib + Siremadli	**Part 1: Ruxolitinib + Siremadli**	**Part 1: Ruxolitinib + Siremadli**	**Part 1: Ruxolitinib + Siremadli**	**Part 1: Ruxolitinib + Rineterkib**	**Part 1: Ruxolitinib + Crizanlizuma**	**Part 1: Ruxolitinib + Sabatolima**	**Part 1: Ruxolitinib +**	**Part 2: Ruxolitinib N = 1**	**All Subjects N = 45**

	n 20 mg N = 7	n 30 mg N = 10	n 40 mg N = 6	n Total N = 23	200 mg N = 9	b N = 6	b N = 2	NIS793 N = 4		
Arm/Group Description	Dose escalation of siremadlin added to existing stable dose of ruxolitinib	Dose escalation of siremadlin added to existing stable dose of ruxolitinib	Dose escalation of siremadlin added to existing stable dose of ruxolitinib	Total	Dose escalation of rineterkib added to existing stable dose of ruxolitinib	Safety run-in of crizanlizumab added to existing stable dose of ruxolitinib	Safety run-in of sabatolimab added to existing stable dose of ruxolitinib	Safety run-in of NIS793 added to existing stable dose of ruxolitinib	Existing stable dose of ruxolitinib as control for Part 2	All Subjects
Total # Affected by any Serious Adverse Event	2	3	4	9	3	1	1	1	0	15
Total # at Risk by any Serious Adverse Event	7	10	6	23	9	6	2	4	1	45
Blood and lymphatic system disorders										
Anaemia	0 (0.00%)	1 (10.00%)	0 (0.00%)	1 (4.35%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Blood loss anaemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Neutropenia	0 (0.00%)	1 (10.00%)	0 (0.00%)	1 (4.35%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Gastrointestinal disorders										
Abdominal pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Diarrhoea	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	1 (2.22%)
Gastritis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (50.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)

Retroperitoneal haemorrhage	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (4.35%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Vomiting	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
General disorders and administration site conditions										
Multiple organ dysfunction syndrome	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (4.35%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Pyrexia	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (4.35%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Infections and infestations										
COVID-19	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (4.35%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Epididymitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (50.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Infection	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (4.35%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Pneumonia	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (4.35%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Injury, poisoning and procedural complications										
Humerus fracture	1 (14.29%)	0 (0.00%)	0 (0.00%)	1 (4.35%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Product administration error	0 (0.00%)	1 (10.00%)	0 (0.00%)	1 (4.35%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)

Investigations										
Body temperature increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	1 (2.22%)
Musculoskeletal and connective tissue disorders										
Back pain	0 (0.00%)	1 (10.00%)	0 (0.00%)	1 (4.35%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Bone pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)										
Prostate cancer	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (4.35%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Renal and urinary disorders										
Cystitis noninfective	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Reproductive system and breast disorders										
Uterine prolapse	1 (14.29%)	0 (0.00%)	0 (0.00%)	1 (4.35%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Respiratory, thoracic and										

mediastinal disorders										
Acute respiratory failure	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Pulmonary embolism	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (4.35%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Skin and subcutaneous tissue disorders										
Neutrophilic dermatosis	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (4.35%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Vascular disorders										
Aortic aneurysm rupture	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Haemorrhage	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (4.35%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)

Other (Not Including Serious) Adverse Events

Time Frame	Adverse events were reported from first dose of study treatment until end of study treatment plus post-treatment safety follow-up, up to a maximum duration of approximately 44 months.
Source Vocabulary for Table Default	MedDRA (27.0)
Collection Approach for Table Default	Systematic Assessment

Frequent Event Reporting Threshold 5%

	Part 1: Ruxolitinib + Siremadlin 20 mg N = 7	Part 1: Ruxolitinib + Siremadlin 30 mg N = 10	Part 1: Ruxolitinib + Siremadlin 40 mg N = 6	Part 1: Ruxolitinib + Siremadlin Total N = 23	Part 1: Ruxolitinib + Rineterkib 200 mg N = 9	Part 1: Ruxolitinib + Crizanlizumab N = 6	Part 1: Ruxolitinib + Sabatolimab N = 2	Part 1: Ruxolitinib + NIS793 N = 4	Part 2: Ruxolitinib N = 1	All Subjects N = 45
Arm/Group Description	Dose escalation of siremadlin added to existing stable dose of ruxolitinib	Dose escalation of siremadlin added to existing stable dose of ruxolitinib	Dose escalation of siremadlin added to existing stable dose of ruxolitinib	Total	Dose escalation of rineterkib added to existing stable dose of ruxolitinib	Safety run-in of crizanlizumab added to existing stable dose of ruxolitinib	Safety run-in of sabatolimab added to existing stable dose of ruxolitinib	Safety run-in of NIS793 added to existing stable dose of ruxolitinib	Existing stable dose of ruxolitinib as control for Part 2	All Subjects
Total # Affected by any Other Adverse Event	7	10	6	23	9	6	2	3	0	43
Total # at Risk by any Other Adverse Event	7	10	6	23	9	6	2	4	1	45
Blood and lymphatic system disorders										
Anaemia	3 (42.86%)	7 (70.00%)	5 (83.33%)	15 (65.22%)	1 (11.11%)	1 (16.67%)	0 (0.00%)	2 (50.00%)	0 (0.00%)	19 (42.22%)
Lymphopenia	1 (14.29%)	1 (10.00%)	0 (0.00%)	2 (8.70%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (6.67%)

Neutropenia	0 (0.00%)	8 (80.00%)	3 (50.00%)	11 (47.83%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	11 (24.44%)
Splenomegaly	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Thrombocytopenia	1 (14.29%)	7 (70.00%)	6 (100.00%)	14 (60.87%)	2 (22.22%)	1 (16.67%)	2 (100.00%)	0 (0.00%)	0 (0.00%)	19 (42.22%)
Cardiac disorders										
Atrial fibrillation	0 (0.00%)	1 (10.00%)	0 (0.00%)	1 (4.35%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Cardiac failure	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Palpitations	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	1 (2.22%)
Pericardial effusion	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Sinus bradycardia	1 (14.29%)	0 (0.00%)	0 (0.00%)	1 (4.35%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Supraventricular tachycardia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Endocrine disorders										
Hyperthyroidism	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Eye disorders										
Dry eye	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	1 (2.22%)
Erythema of eyelid	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	1 (2.22%)
Eye pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	1 (2.22%)
Macular oedema	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)

Photopsia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Presbyopia	1 (14.29%)	0 (0.00%)	0 (0.00%)	1 (4.35%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Retinal detachment	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Retinal haemorrhage	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (4.35%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Retinopathy	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (22.22%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (4.44%)
Serous retinopathy	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Visual acuity reduced	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Visual impairment	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (4.35%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Gastrointestinal disorders										
Abdominal discomfort	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (4.35%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (4.44%)
Abdominal distension	0 (0.00%)	1 (10.00%)	0 (0.00%)	1 (4.35%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Abdominal pain	1 (14.29%)	1 (10.00%)	0 (0.00%)	2 (8.70%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (6.67%)
Abdominal pain upper	1 (14.29%)	1 (10.00%)	0 (0.00%)	2 (8.70%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (4.44%)
Constipation	1 (14.29%)	2 (20.00%)	1 (16.67%)	4 (17.39%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	5 (11.11%)
Diarrhoea	3 (42.86%)	2 (20.00%)	0 (0.00%)	5 (21.74%)	6 (66.67%)	2 (33.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	13 (28.89%)
Dry mouth	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	2 (4.44%)

Flatulence	1 (14.29%)	0 (0.00%)	0 (0.00%)	1 (4.35%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Gingival bleeding	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Mouth haemorrhage	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	1 (2.22%)
Nausea	6 (85.71%)	4 (40.00%)	3 (50.00%)	13 (56.52%)	3 (33.33%)	2 (33.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	18 (40.00%)
Oral dysaesthesia	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (4.35%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Vomiting	1 (14.29%)	2 (20.00%)	0 (0.00%)	3 (13.04%)	1 (11.11%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	5 (11.11%)
General disorders and administration site conditions										
Asthenia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (33.33%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	4 (8.89%)
Chest discomfort	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Chest pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (33.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (4.44%)
Chills	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	2 (4.44%)
Discomfort	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (4.35%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Fatigue	5 (71.43%)	1 (10.00%)	2 (33.33%)	8 (34.78%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	8 (17.78%)
Malaise	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Mucosal inflammation	1 (14.29%)	0 (0.00%)	0 (0.00%)	1 (4.35%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Oedema peripheral	1 (14.29%)	1 (10.00%)	1 (16.67%)	3 (13.04%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	4 (8.89%)

Pyrexia	0 (0.00%)	3 (30.00%)	2 (33.33%)	5 (21.74%)	1 (11.11%)	1 (16.67%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	8 (17.78%)
Infections and infestations										
Bronchitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Candida infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	1 (2.22%)
COVID-19	0 (0.00%)	2 (20.00%)	1 (16.67%)	3 (13.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (6.67%)
Erysipelas	0 (0.00%)	1 (10.00%)	0 (0.00%)	1 (4.35%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Eye infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	1 (2.22%)
Furuncle	0 (0.00%)	1 (10.00%)	0 (0.00%)	1 (4.35%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Mucosal infection	0 (0.00%)	1 (10.00%)	0 (0.00%)	1 (4.35%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Nasopharyngitis	1 (14.29%)	0 (0.00%)	0 (0.00%)	1 (4.35%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (4.44%)
Oral herpes	0 (0.00%)	1 (10.00%)	0 (0.00%)	1 (4.35%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Tooth infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	1 (2.22%)
Upper respiratory tract infection	2 (28.57%)	0 (0.00%)	0 (0.00%)	2 (8.70%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (4.44%)
Urinary tract infection	0 (0.00%)	1 (10.00%)	0 (0.00%)	1 (4.35%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (4.44%)
Wound infection	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (4.35%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)

Injury, poisoning and procedural complications										
Contusion	0 (0.00%)	1 (10.00%)	0 (0.00%)	1 (4.35%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	2 (4.44%)
Fall	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (4.44%)
Incorrect dose administered	0 (0.00%)	1 (10.00%)	0 (0.00%)	1 (4.35%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Ligament sprain	1 (14.29%)	0 (0.00%)	0 (0.00%)	1 (4.35%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Skin abrasion	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Skin wound	0 (0.00%)	1 (10.00%)	0 (0.00%)	1 (4.35%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Tendon rupture	1 (14.29%)	0 (0.00%)	0 (0.00%)	1 (4.35%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Transfusion reaction	0 (0.00%)	1 (10.00%)	0 (0.00%)	1 (4.35%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Investigations										
Alanine aminotransferase increased	0 (0.00%)	1 (10.00%)	1 (16.67%)	2 (8.70%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (6.67%)
Amylase increased	1 (14.29%)	1 (10.00%)	0 (0.00%)	2 (8.70%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (6.67%)
Blood alkaline phosphatase increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Blood creatine phosphokinase increased	1 (14.29%)	0 (0.00%)	0 (0.00%)	1 (4.35%)	2 (22.22%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (6.67%)

Blood creatinine increased	0 (0.00%)	1 (10.00%)	0 (0.00%)	1 (4.35%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (4.44%)
Blood folate decreased	0 (0.00%)	1 (10.00%)	0 (0.00%)	1 (4.35%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (4.44%)
Blood potassium increased	1 (14.29%)	0 (0.00%)	0 (0.00%)	1 (4.35%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Cardiac murmur	1 (14.29%)	0 (0.00%)	0 (0.00%)	1 (4.35%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (4.44%)
Heart rate decreased	1 (14.29%)	0 (0.00%)	0 (0.00%)	1 (4.35%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Heart sounds abnormal	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Lipase increased	1 (14.29%)	1 (10.00%)	0 (0.00%)	2 (8.70%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (6.67%)
Neutrophil count decreased	1 (14.29%)	0 (0.00%)	0 (0.00%)	1 (4.35%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Platelet count decreased	1 (14.29%)	0 (0.00%)	0 (0.00%)	1 (4.35%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
SARS-CoV-2 test positive	0 (0.00%)	1 (10.00%)	0 (0.00%)	1 (4.35%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Weight increased	0 (0.00%)	1 (10.00%)	1 (16.67%)	2 (8.70%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (4.44%)
White blood cell count decreased	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (4.35%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Metabolism and nutrition disorders										
Decreased appetite	3 (42.86%)	0 (0.00%)	0 (0.00%)	3 (13.04%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	4 (8.89%)
Dehydration	1 (14.29%)	0 (0.00%)	0 (0.00%)	1 (4.35%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Gout	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)

Hyperkalaemia	1 (14.29%)	1 (10.00%)	0 (0.00%)	2 (8.70%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (4.44%)
Hyperuricaemia	1 (14.29%)	2 (20.00%)	1 (16.67%)	4 (17.39%)	1 (11.11%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	6 (13.33%)
Hypokalaemia	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (4.35%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Hyponatraemia	0 (0.00%)	1 (10.00%)	0 (0.00%)	1 (4.35%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Iron overload	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (4.35%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Musculoskeletal and connective tissue disorders										
Arthralgia	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (4.35%)	2 (22.22%)	2 (33.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	5 (11.11%)
Arthropathy	1 (14.29%)	0 (0.00%)	0 (0.00%)	1 (4.35%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Back pain	1 (14.29%)	0 (0.00%)	0 (0.00%)	1 (4.35%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (4.44%)
Bone pain	1 (14.29%)	0 (0.00%)	0 (0.00%)	1 (4.35%)	2 (22.22%)	1 (16.67%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	5 (11.11%)
Gouty arthritis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Muscle spasms	1 (14.29%)	0 (0.00%)	0 (0.00%)	1 (4.35%)	1 (11.11%)	1 (16.67%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	4 (8.89%)
Muscle tightness	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (4.35%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Muscular weakness	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Pain in extremity	1 (14.29%)	0 (0.00%)	0 (0.00%)	1 (4.35%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Sacroiliac joint dysfunction	1 (14.29%)	0 (0.00%)	0 (0.00%)	1 (4.35%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Neoplasms benign, malignant and										

unspecified (incl cysts and polyps)										
Basal cell carcinoma	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (4.35%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	2 (4.44%)
Squamous cell carcinoma	1 (14.29%)	0 (0.00%)	0 (0.00%)	1 (4.35%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Squamous cell carcinoma of skin	1 (14.29%)	0 (0.00%)	0 (0.00%)	1 (4.35%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Nervous system disorders										
Dizziness	1 (14.29%)	0 (0.00%)	1 (16.67%)	2 (8.70%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (6.67%)
Dysaesthesia	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (4.35%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Dysgeusia	0 (0.00%)	0 (0.00%)	2 (33.33%)	2 (8.70%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	4 (8.89%)
Headache	3 (42.86%)	1 (10.00%)	0 (0.00%)	4 (17.39%)	1 (11.11%)	2 (33.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	7 (15.56%)
Migraine	1 (14.29%)	0 (0.00%)	0 (0.00%)	1 (4.35%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Paraesthesia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Peripheral sensory neuropathy	0 (0.00%)	1 (10.00%)	0 (0.00%)	1 (4.35%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Polyneuropathy	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Sciatica	1 (14.29%)	0 (0.00%)	0 (0.00%)	1 (4.35%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Psychiatric disorders										
Anxiety	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (4.35%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Confusional state	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (4.35%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)

Insomnia	0 (0.00%)	0 (0.00%)	2 (33.33%)	2 (8.70%)	1 (11.11%)	2 (33.33%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	6 (13.33%)
Sleep disorder	0 (0.00%)	1 (10.00%)	0 (0.00%)	1 (4.35%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Renal and urinary disorders										
Dysuria	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (4.35%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Renal failure	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (4.35%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Respiratory, thoracic and mediastinal disorders										
Cough	2 (28.57%)	0 (0.00%)	0 (0.00%)	2 (8.70%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (6.67%)
Dyspnoea	1 (14.29%)	0 (0.00%)	1 (16.67%)	2 (8.70%)	0 (0.00%)	2 (33.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	4 (8.89%)
Dyspnoea exertional	0 (0.00%)	1 (10.00%)	0 (0.00%)	1 (4.35%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (4.44%)
Epistaxis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11%)	1 (16.67%)	0 (0.00%)	2 (50.00%)	0 (0.00%)	4 (8.89%)
Hypoxia	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (4.35%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Nasal cavity mass	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	1 (2.22%)
Skin and subcutaneous tissue disorders										
Actinic keratosis	1 (14.29%)	0 (0.00%)	0 (0.00%)	1 (4.35%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Alopecia	1 (14.29%)	0 (0.00%)	0 (0.00%)	1 (4.35%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Blister	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)

Dermatitis acneiform	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Dry skin	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Night sweats	1 (14.29%)	0 (0.00%)	1 (16.67%)	2 (8.70%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	3 (6.67%)
Pain of skin	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Pruritus	0 (0.00%)	1 (10.00%)	0 (0.00%)	1 (4.35%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	3 (6.67%)
Rash	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (22.22%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (4.44%)
Rash maculo-papular	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Skin discolouration	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Skin disorder	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	1 (2.22%)
Skin lesion	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (4.35%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Skin ulcer	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (4.35%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Trichodysplasia spinulosa	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	1 (2.22%)
Vascular disorders										
Angiopathy	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Capillary leak syndrome	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (4.35%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)
Hypertension	4 (57.14%)	0 (0.00%)	0 (0.00%)	4 (17.39%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	5 (11.11%)
Hypotension	1 (14.29%)	0 (0.00%)	0 (0.00%)	1 (4.35%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)

Venous thrombosis	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (4.35%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)

Other Relevant Findings

Not applicable

Conclusion:

In the extension phase, the treatment group receiving ruxolitinib + siremadlin showed a 100% reduction in spleen length across all participants, with spleen volume reductions, ranging from 28.5% to 70.6%. In contrast, the ruxolitinib + rineterkib group exhibited a 72.2% reduction in spleen length and an 80.2% reduction in spleen volume. Safety findings in the study were consistent with the known safety profiles of the study drugs as single agents, and no new or unexpected safety signals were identified in combination.

Date of Clinical Trial Report

04 February 2025