Clinical trial results:
A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of Navitoclax in Combination with Ruxolitinib Versus Ruxolitinib in Subjects with Myelofibrosis (TRANSFORM-1)

Summary

EudraCT number	2020-000097-15
Trial protocol	GB FR DE SE NL AT BE GR IT BG HR
Global end of trial date	29 January 2025

Results information

Result version number	v1 (current)
This version publication date	01 February 2026
First version publication date	01 February 2026

Trial information

Trial identification

Sponsor protocol code	M16-191

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04472598
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AbbVie Deutschland GmbH & Co. KG
Sponsor organisation address	AbbVie House, Vanwall Business Park, Vanwall Road, Maidenhead, Berkshire, United Kingdom, SL6 4UB
Public contact	Global Medical Services, AbbVie, 001 8006339110, abbvieclinicaltrials@abbvie.com
Scientific contact	Global Medical Services, AbbVie, 001 8006339110, abbvieclinicaltrials@abbvie.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	29 January 2025
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 January 2025
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Myelofibrosis is a type of bone marrow cancer that usually develops slowly and disrupts body's normal production of blood cells. It causes bone marrow scarring, leading to severe anemia that can cause weakness and fatigue. It can also cause a low number of blood-clotting cells called platelets, which increases risk of bleeding. Myelofibrosis often causes an enlarged spleen. The purpose of this study is to see if a combination of navitoclax and ruxolitinib is more effective and safe in assessment of change in spleen volume when compared to ruxolitinib in participants with myelofibrosis.

Participants will receive oral navitoclax tablet with oral ruxolitinib tablet or oral ruxolitinib tablet with oral placebo (no active drug) tablet and treatment may continue until the participant cannot tolerate the study drug, or benefit is not achieved, or other reasons which qualify for discontinuation of the study drug.

Protection of trial subjects:

Subjects must voluntarily sign and date an informed consent (or their legally authorized representative can sign and date the informed consent upon subject's understanding of the consent, if permitted by local regulations), approved by an independent ethics committee (IEC)/institutional review board (IRB) prior to the initiation of any Screening or study-specific procedures.

Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	29 September 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Serbia: 7
Country: Number of subjects enrolled	South Africa: 2
Country: Number of subjects enrolled	Spain: 14
Country: Number of subjects enrolled	Australia: 10
Country: Number of subjects enrolled	Austria: 3
Country: Number of subjects enrolled	Belgium: 9
Country: Number of subjects enrolled	Bulgaria: 9
Country: Number of subjects enrolled	Canada: 6
Country: Number of subjects enrolled	Croatia: 3
Country: Number of subjects enrolled	France: 14
Country: Number of subjects enrolled	Germany: 3

Country: Number of subjects enrolled	Greece: 2
Country: Number of subjects enrolled	Israel: 20
Country: Number of subjects enrolled	Italy: 20
Country: Number of subjects enrolled	Japan: 21
Country: Number of subjects enrolled	Korea, Republic of: 13
Country: Number of subjects enrolled	Netherlands: 5
Country: Number of subjects enrolled	Russian Federation: 22
Country: Number of subjects enrolled	Sweden: 3
Country: Number of subjects enrolled	Taiwan: 13
Country: Number of subjects enrolled	Türkiye: 11
Country: Number of subjects enrolled	Ukraine: 7
Country: Number of subjects enrolled	United Kingdom: 6
Country: Number of subjects enrolled	United States: 29
Worldwide total number of subjects	252
EEA total number of subjects	85

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	69
From 65 to 84 years	179
85 years and over	4

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The study included a 28-day Screening period.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo for Navitoclax + Ruxolitinib

Arm description:

Placebo for navitoclax tablets were administered orally once daily (QD) per Baseline platelet count (>150 × 10^9/L starting dose of 200 mg; ≤150 × 10^9/L starting dose of 100 mg, which could be increased to 200 mg QD after 7 days provided platelet count is ≥75 × 10^9/L). Placebo for navitoclax didn't exceed 200 mg QD for first 24 weeks of treatment. After Week 25, Day 1 visit, placebo for navitoclax dose may be increased to 300 mg QD at Investigator's discretion for those with suboptimal spleen response defined as failure to achieve spleen volume reduction of at least 10% per imaging. Ruxolitinib tablets were administered orally twice daily (BID) per Baseline platelet count (>200 × 10^9/L starting dose of 20 mg; 100-200 × 10^9/L starting dose of 15 mg). Participants will continue their treatment until end of clinical benefit, unacceptable toxicity, or they meet other protocol criteria for discontinuation (whichever occurs first).

Arm type	Active comparator
Investigational medicinal product name	Placebo for Navitoclax
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Film-coated tablet; Oral

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

Dosage and administration details:

Tablet; Oral

Arm title	Navitoclax + Ruxolitinib

Arm description:

Navitoclax tablets were administered orally once daily (QD) per Baseline platelet count (>150 × 10^9/L starting dose of 200 mg; ≤150 × 10^9/L starting dose of 100 mg, which could be increased to 200 mg QD after 7 days provided platelet count is ≥75 × 10^9/L). Navitoclax didn't exceed 200 mg QD for first 24 weeks of treatment. After Week 25, Day 1 visit, navitoclax dose may be increased to 300 mg QD at Investigator's discretion for those with suboptimal spleen response defined as failure to achieve spleen volume reduction of at least 10% per imaging. Ruxolitinib tablets were administered orally twice daily (BID) per Baseline platelet count (>200 × 10^9/L starting dose of 20 mg; 100-200 × 10^9/L starting dose of 15 mg). Participants will continue their treatment until end of clinical benefit, unacceptable toxicity, or they meet other protocol criteria for discontinuation (whichever occurs first).

Arm type	Experimental
Investigational medicinal product name	Ruxolitinib
Investigational medicinal product code	
Other name	Jakafi
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:
Tablet; Oral

Investigational medicinal product name	Navitoclax
Investigational medicinal product code	
Other name	ABT-263
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:
Film-coated tablet; Oral

Number of subjects in period 1	Placebo for Navitoclax + Ruxolitinib	Navitoclax + Ruxolitinib
Started	127	125
Completed	0	0
Not completed	127	125
Death	28	35
Other, not specified	83	81
Lost to follow-up	1	2
Withdrew consent	15	7

Baseline characteristics

Reporting groups	
Reporting group title	Placebo for Navitoclax + Ruxolitinib

Reporting group description:

Placebo for navitoclax tablets were administered orally once daily (QD) per Baseline platelet count (>150 × 10^9/L starting dose of 200 mg; ≤150 × 10^9/L starting dose of 100 mg, which could be increased to 200 mg QD after 7 days provided platelet count is ≥75 × 10^9/L). Placebo for navitoclax didn't exceed 200 mg QD for first 24 weeks of treatment. After Week 25, Day 1 visit, placebo for navitoclax dose may be increased to 300 mg QD at Investigator's discretion for those with suboptimal spleen response defined as failure to achieve spleen volume reduction of at least 10% per imaging. Ruxolitinib tablets were administered orally twice daily (BID) per Baseline platelet count (>200 × 10^9/L starting dose of 20 mg; 100-200 × 10^9/L starting dose of 15 mg). Participants will continue their treatment until end of clinical benefit, unacceptable toxicity, or they meet other protocol criteria for discontinuation (whichever occurs first).

Reporting group title	Navitoclax + Ruxolitinib

Reporting group description:

Navitoclax tablets were administered orally once daily (QD) per Baseline platelet count (>150 × 10^9/L starting dose of 200 mg; ≤150 × 10^9/L starting dose of 100 mg, which could be increased to 200 mg QD after 7 days provided platelet count is ≥75 × 10^9/L). Navitoclax didn't exceed 200 mg QD for first 24 weeks of treatment. After Week 25, Day 1 visit, navitoclax dose may be increased to 300 mg QD at Investigator's discretion for those with suboptimal spleen response defined as failure to achieve spleen volume reduction of at least 10% per imaging. Ruxolitinib tablets were administered orally twice daily (BID) per Baseline platelet count (>200 × 10^9/L starting dose of 20 mg; 100-200 × 10^9/L starting dose of 15 mg). Participants will continue their treatment until end of clinical benefit, unacceptable toxicity, or they meet other protocol criteria for discontinuation (whichever occurs first).

Reporting group values	Placebo for Navitoclax + Ruxolitinib	Navitoclax + Ruxolitinib	Total
Number of subjects	127	125	252
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	68.5	68.7	
standard deviation	± 8.49	± 9.17	-
Gender categorical Units: Subjects			
Female	46	62	108
Male	81	63	144
Ethnicity Units: Subjects			
Hispanic or Latino	8	7	15
Not Hispanic or Latino	119	118	237
Unknown or Not Reported	0	0	0
Race Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	26	24	50
Native Hawaiian or Other Pacific Islander	1	0	1
Black or African American	1	1	2
White	99	100	199

More than one race	0	0	0
Unknown or Not Reported	0	0	0

End points

End points reporting groups

Reporting group title	Placebo for Navitoclax + Ruxolitinib

Reporting group description:

Placebo for navitoclax tablets were administered orally once daily (QD) per Baseline platelet count (>150 × 10^9/L starting dose of 200 mg; ≤150 × 10^9/L starting dose of 100 mg, which could be increased to 200 mg QD after 7 days provided platelet count is ≥75 × 10^9/L). Placebo for navitoclax didn't exceed 200 mg QD for first 24 weeks of treatment. After Week 25, Day 1 visit, placebo for navitoclax dose may be increased to 300 mg QD at Investigator's discretion for those with suboptimal spleen response defined as failure to achieve spleen volume reduction of at least 10% per imaging. Ruxolitinib tablets were administered orally twice daily (BID) per Baseline platelet count (>200 × 10^9/L starting dose of 20 mg; 100-200 × 10^9/L starting dose of 15 mg). Participants will continue their treatment until end of clinical benefit, unacceptable toxicity, or they meet other protocol criteria for discontinuation (whichever occurs first).

Reporting group title	Navitoclax + Ruxolitinib

Reporting group description:

Navitoclax tablets were administered orally once daily (QD) per Baseline platelet count (>150 × 10^9/L starting dose of 200 mg; ≤150 × 10^9/L starting dose of 100 mg, which could be increased to 200 mg QD after 7 days provided platelet count is ≥75 × 10^9/L). Navitoclax didn't exceed 200 mg QD for first 24 weeks of treatment. After Week 25, Day 1 visit, navitoclax dose may be increased to 300 mg QD at Investigator's discretion for those with suboptimal spleen response defined as failure to achieve spleen volume reduction of at least 10% per imaging. Ruxolitinib tablets were administered orally twice daily (BID) per Baseline platelet count (>200 × 10^9/L starting dose of 20 mg; 100-200 × 10^9/L starting dose of 15 mg). Participants will continue their treatment until end of clinical benefit, unacceptable toxicity, or they meet other protocol criteria for discontinuation (whichever occurs first).

Primary: Percentage of Participants With ≥ 35% Reduction From Baseline in Spleen Volume at Week 24 (SVR35W24)

End point title	Percentage of Participants With ≥ 35% Reduction From Baseline in Spleen Volume at Week 24 (SVR35W24)

End point description:

Reduction in spleen volume is measured by magnetic resonance imaging (MRI) or computed tomography (CT), per International Working Group (IWG) criteria.

Analysis Population: Intent-to-Treat population: all randomized participants analyzed by the treatment arm assigned at the time of randomization

End point type	Primary

End point timeframe:

Baseline, Week 24

End point values	Placebo for Navitoclax + Ruxolitinib	Navitoclax + Ruxolitinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	127	125		
Units: percentage of participants				
number (confidence interval 95%)	31.50 (23.55 to 40.33)	63.20 (54.11 to 71.65)		

Statistical analyses

Statistical analysis title	Navitoclax + Ruxolitinib vs Placebo for Navitoclax

Statistical analysis description:

The percentage of participants who achieved SVR35W24 was compared between the treatment arms using the Cochran-Mantel-Haenszel (CMH) test, stratified by DIPSS+ risk group (intermediate versus high risk) and platelet count (≤ 200 × 10^9 /L versus > 200 × 10^9 /L) collected in the Electronic Data Capture (EDC) system.

Comparison groups	Navitoclax + Ruxolitinib v Placebo for Navitoclax + Ruxolitinib
Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [1]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Response Rate Difference
Point estimate	30.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	19.38
upper limit	42.5

Notes:

[1] - Navitoclax + Ruxolitinib - Placebo for Navitoclax + Ruxolitinib

Secondary: Change From Baseline in Total Symptom Score (TSS) at Week 24 as Measured by Myelofibrosis Symptom Assessment Form (MFSAF) v4.0

End point title	Change From Baseline in Total Symptom Score (TSS) at Week 24 as Measured by Myelofibrosis Symptom Assessment Form (MFSAF) v4.0

End point description:

TSS is assessed by the Myelofibrosis Symptom Assessment Form (MFSAF) version 4.0. Participants complete a symptom diary and rate the following seven MF symptoms: fatigue, night sweats, abdominal discomfort, pruritus, pain under the ribs on the left side, early satiety, and bone pain daily using a scale from 0 (absent) to 10 (worst imaginable), and the scores are averaged over 7 days, with a minimum of 4 days required to calculate the average score. Participants for whom a valid average score cannot be calculated either at baseline or post-baseline are considered non-responders. The TSS reflects the sum of the scores of these symptoms, for a maximum possible score of 70 (i.e., most severe symptom experience). Negative changes from Baseline indicate improvement.

Analysis Population: Intent-to-Treat population: all randomized participants analyzed by the treatment arm assigned at the time of randomization

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo for Navitoclax + Ruxolitinib	Navitoclax + Ruxolitinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	127	125		
Units: units on a scale				
least squares mean (confidence interval 95%)	-11.14 (-13.23 to -9.05)	-9.71 (-11.80 to -7.62)		

Statistical analyses

Statistical analysis title	Navitoclax + Ruxolitinib vs Placebo for Navitoclax

Statistical analysis description:

A linear mixed effects regression model with an unstructured variance covariance matrix was used to test the change from the baseline in scores between the treatment arms. The model included the following factors: Baseline score, calculated DIPSS+ risk group (intermediate versus high risk), Baseline platelet count (<= 200 × 10^9/L versus > 200 × 10^9/L), treatment arm, visit and treatment arm by visit interaction.

Comparison groups	Placebo for Navitoclax + Ruxolitinib v Navitoclax + Ruxolitinib
Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2852 [2]
Method	Regression, Linear
Parameter estimate	LS Mean Difference
Point estimate	1.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	4.06
Variability estimate	Standard error of the mean
Dispersion value	1.33

Notes:

[2] - Navitoclax + Ruxolitinib - Placebo for Navitoclax + Ruxolitinib

Secondary: Percentage of Participants With ≥ 35% Reduction From Baseline in Spleen Volume (SVR35) at Any Time

End point title	Percentage of Participants With ≥ 35% Reduction From Baseline in Spleen Volume (SVR35) at Any Time

End point description:

Reduction in spleen volume is measured by magnetic resonance imaging (MRI) or computed tomography (CT), per International Working Group (IWG) criteria.

Analysis Population: Intent-to-Treat population: all randomized participants analyzed by the treatment arm assigned at the time of randomization

End point type	Secondary

End point timeframe:

Up to Week 97

End point values	Placebo for Navitoclax + Ruxolitinib	Navitoclax + Ruxolitinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	127	125		
Units: percentage of participants				
number (confidence interval 95%)	44.09 (35.30 to 53.17)	76.80 (68.41 to 83.88)		

Statistical analyses

Statistical analysis title	Navitoclax + Ruxolitinib vs Placebo for Navitoclax

Statistical analysis description:

The percentage of participants who achieved SVR35 was compared between the treatment arms using the Cochran-Mantel-Haenszel (CMH) test, stratified by DIPSS+ risk group (intermediate versus high risk) and platelet count (≤ 200 × 10^9 /L versus > 200 × 10^9 /L) collected in the Electronic Data Capture (EDC) system.

Comparison groups	Placebo for Navitoclax + Ruxolitinib v Navitoclax + Ruxolitinib
Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [3]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Response Rate Difference
Point estimate	32.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	21.16
upper limit	43.12

Notes:

[3] - Navitoclax + Ruxolitinib - Placebo for Navitoclax + Ruxolitinib

Secondary: Duration of 35% Spleen Volume Reduction (SVR35)

End point title	Duration of 35% Spleen Volume Reduction (SVR35)

End point description:

Duration of SVR35 is defined as the time between the date of first response of spleen volume reduction of 35% achievement to the date of the first assessment where the spleen volume is less than 35% reduction from Baseline and is at least 25% increase from the nadir (the lowest spleen volume), confirmed relapse, or leukemic transformation per International Working Group (IWG) criteria, whichever is earlier.

99999 in the data table below indicates not calculable/estimable due to low number of events.

Analysis Population: Intent-to-Treat population: all randomized participants analyzed by the treatment arm assigned at the time of randomization; only participants who achieve SVR35 are included in the analysis

End point type	Secondary

End point timeframe:

Baseline (Week 0) Up to Month 48

End point values	Placebo for Navitoclax + Ruxolitinib	Navitoclax + Ruxolitinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56	96		
Units: months				
median (confidence interval 95%)	99999 (19.38 to 99999)	99999 (27.60 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline In Fatigue at Week 24 as Measured by the PROMIS Fatigue Short Form (SF) 7a

End point title	Change From Baseline In Fatigue at Week 24 as Measured by the PROMIS Fatigue Short Form (SF) 7a

End point description:

The PROMIS Fatigue SF 7a is a 7-item questionnaire that assesses the impact and experience of fatigue over the past 7 days. All questions employ the following five response options: 1 = Never, 2 = Rarely, 3 = Sometimes, 4 = Often, and 5 = Always, with 7 questions for a total maximum score of 35. Negative changes from Baseline indicate improvement.

Analysis Population: Intent-to-Treat population: all randomized participants analyzed by the treatment arm assigned at the time of randomization; only participants with both Baseline and Week 24 score are included in the analysis

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo for Navitoclax + Ruxolitinib	Navitoclax + Ruxolitinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	104		
Units: units on a scale				
least squares mean (confidence interval 95%)	-3.63 (-5.38 to -1.88)	-3.75 (-5.46 to -2.04)		

Statistical analyses

Statistical analysis title	Navitoclax + Ruxolitinib vs Placebo for Navitoclax

Statistical analysis description:

A linear mixed effects regression model with a compound symmetry variance covariance matrix was used to test the change from the baseline in scores between the treatment arms. The model included

following factors: Baseline score, calculated DIPSS+ risk group (intermediate versus high risk), Baseline platelet count (≤ 200 × 10^9/L versus > 200 × 10^9/L), treatment arm, visit and treatment arm by visit interaction.

Comparison groups	Placebo for Navitoclax + Ruxolitinib v Navitoclax + Ruxolitinib
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9029 [4]
Method	Regression, Linear
Parameter estimate	LS Mean Difference
Point estimate	-0.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.03
upper limit	1.8
Variability estimate	Standard error of the mean
Dispersion value	0.975

Notes:

[4] - Navitoclax + Ruxolitinib - Placebo for Navitoclax + Ruxolitinib

Secondary: Change From Baseline at Week 24 in Physical Functioning as Measured by the Physical Functioning Domain of the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30

End point title	Change From Baseline at Week 24 in Physical Functioning as Measured by the Physical Functioning Domain of the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30

End point description:

EORTC QLQ-C30 is a 30-item participant self-report questionnaire composed of both multi-item and single scales, including a physical functioning scale. Participants rate items and a score ranging from 0 to 100 is calculated. A higher score on the physical functioning scale indicates a better level of functioning, and positive changes from Baseline indicate improvement.

Analysis Population: Intent-to-Treat population: all randomized participants analyzed by the treatment arm assigned at the time of randomization; only participants with both Baseline and Week 24 score are included in the analysis

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo for Navitoclax + Ruxolitinib	Navitoclax + Ruxolitinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	95	99		
Units: units on a scale				
least squares mean (confidence interval 95%)	6.198 (2.238 to 10.158)	7.326 (3.458 to 11.195)		

Statistical analyses

Statistical analysis title	Navitoclax + Ruxolitinib vs Placebo for Navitoclax

Statistical analysis description:

A linear mixed effects regression model with a compound symmetry variance covariance structure was used to fit the longitudinal data. The model includes following factors: Baseline score, calculated DIPSS+ risk group (intermediate versus high risk), Baseline platelet count (≤ 200 × 10^9/L versus > 200 × 10^9/L), treatment arm, visit and treatment arm by visit interaction.

Comparison groups	Placebo for Navitoclax + Ruxolitinib v Navitoclax + Ruxolitinib
Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6152 [5]
Method	Regression, Linear
Parameter estimate	LS Mean Difference
Point estimate	1.129
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.278
upper limit	5.536
Variability estimate	Standard error of the mean
Dispersion value	2.2436

Notes:

[5] - Navitoclax + Ruxolitinib - Placebo for Navitoclax + Ruxolitinib

Secondary: Percentage of Participants Achieving Anemia Response

End point title	Percentage of Participants Achieving Anemia Response

End point description:

Transfusion independent (TI) at Baseline (BL) w/ hemoglobin (Hb) value < 10 g/dL: anemia response achieved if post-BL Hb increases by ≥2 g/dL w/out receiving packed red blood cells (PRBC) transfusion w/in 2 wks and w/out erythropoietin/mimetics w/in last 4 wks prior to increase in Hb level by ≥2g/dL. Hb values > 30 d after last dose of study Tx or after start of post-study Tx or disease progression, whichever is earlier, not considered in anemia response analysis.

Transfusion dependent (TD) at BL: anemia response is a period of at least 12 consecutive wks w/out PRBC transfusion at any time after first dose of study drug and on or prior to 30 d post last dose of study drug, the start of post-study Tx, disease progression or death, whichever occurs earlier.

Analysis Population: all randomized participants analyzed by Tx arm assigned; those who were BL transfusion independent with BL Hb of ≥10 g/dL were excluded from analysis since they were not evaluable for anemia response

End point type	Secondary

End point timeframe:

Up to Week 97

End point values	Placebo for Navitoclax + Ruxolitinib	Navitoclax + Ruxolitinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	72	66		
Units: percentage of participants				
number (confidence interval 95%)				
Overall (n= 72,66)	30.56 (20.24 to 42.53)	28.79 (18.30 to 41.25)		
BL transfusion indep. w/ BL Hb <10 g/dL (n= 68,61)	29.41 (18.98 to 41.71)	29.51 (18.52 to 42.57)		
BL transfusion dependent (n= 4,5)	50.00 (6.76 to 93.24)	20.00 (0.51 to 71.64)		

Statistical analyses

Statistical analysis title	Overall

Statistical analysis description:

P-value is from Cochran-Mantel-Haenszel (CMH) test, stratified by calculated DIPSS+ risk group (intermediate versus high risk) and Baseline platelet count (≤ 200 × 10^9/L versus > 200 × 10^9/L) reported in the Electronic Data Capture (EDC) system.

Comparison groups	Placebo for Navitoclax + Ruxolitinib v Navitoclax + Ruxolitinib
Number of subjects included in analysis	138
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8524 [6]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Response Rate Difference
Point estimate	-1.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.57
upper limit	13.7

Notes:

[6] - Navitoclax + Ruxolitinib - Placebo for Navitoclax + Ruxolitinib

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS is defined as the time from the date of randomization to the date of death from any cause.

In the table below, 9999 and 99999 = not calculable/estimable due to low number of events.

Analysis Population: Intent-to-Treat population: all randomized participants analyzed by the treatment arm assigned at the time of randomization

End point type	Secondary

End point timeframe:

Up to 50 months

End point values	Placebo for Navitoclax + Ruxolitinib	Navitoclax + Ruxolitinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	127	125		
Units: months				
median (confidence interval 95%)	48.49 (48.49 to 99999)	9999 (41.36 to 99999)		

Statistical analyses

Statistical analysis title	Navitoclax + Ruxolitinib vs Placebo for Navitoclax

Statistical analysis description:

Overall survival was analyzed using Kaplan-Meier methodology and compared between treatment arms using the log-rank test, stratified by DIPSS+ risk group (intermediate versus high risk) and platelet count (≤ 200 × 10^9 /L versus > 200 × 10^9 /L) reported in the Electronic Data Capture (EDC) system.

Comparison groups	Placebo for Navitoclax + Ruxolitinib v Navitoclax + Ruxolitinib
Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3867
Method	Log Rank

Secondary: Leukemia-Free Survival

End point title	Leukemia-Free Survival

End point description:

Leukemia-free survival is defined as the number of days from the date of randomization to the onset date of documented leukemia, disease progression due to leukemia, or death due to leukemia, whichever occurs first.

In the table below, 9999 and 99999 = not calculable/estimable due to low number of events.

Analysis Population: Intent-to-Treat population: all randomized participants analyzed by the treatment arm assigned at the time of randomization

End point type	Secondary

End point timeframe:

Up to 50 months

End point values	Placebo for Navitoclax + Ruxolitinib	Navitoclax + Ruxolitinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	127	125		
Units: months				
median (confidence interval 95%)	9999 (40.05 to 99999)	9999 (37.62 to 99999)		

Statistical analyses

Statistical analysis title	Navitoclax + Ruxolitinib vs Placebo for Navitoclax

Statistical analysis description:

Leukemia-Free survival was analyzed using Kaplan-Meier methodology and compared between treatment arms using the log-rank test, stratified by DIPSS+ risk group (intermediate versus high risk) and platelet count (≤ 200 × 10^9 /L versus > 200 × 10^9 /L) reported in the Electronic Data Capture (EDC) system.

Comparison groups	Placebo for Navitoclax + Ruxolitinib v Navitoclax + Ruxolitinib
Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9706
Method	Log Rank

Secondary: Percentage of Participants Who Achieved Reduction in Grade of Bone Marrow Fibrosis From Baseline at Any Time

End point title	Percentage of Participants Who Achieved Reduction in Grade of Bone Marrow Fibrosis From Baseline at Any Time

End point description:

Change in grade of bone marrow fibrosis was measured per the European consensus grading system through bone marrow biopsy. The percentage of participants who achieved reduction of at least 1 grade in bone marrow fibrosis compared to Baseline is reported.

Analysis Population: Intent-to-Treat population: all randomized participants analyzed by the treatment arm assigned at the time of randomization; participants who have a bone marrow fibrosis grade determined at Baseline and at least one post-Baseline assessment are included in the analysis

End point type	Secondary

End point timeframe:

Up to Week 97

End point values	Placebo for Navitoclax + Ruxolitinib	Navitoclax + Ruxolitinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90	92		
Units: percentage of participants				
number (confidence interval 95%)	48.89 (38.20 to 59.65)	56.52 (45.78 to 66.83)		

Statistical analyses

Statistical analysis title	Navitoclax + Ruxolitinib vs Placebo for Navitoclax

Statistical analysis description:

P-value is from Cochran-Mantel-Haenszel (CMH) test, stratified by calculated DIPSS+ risk group (intermediate versus high risk) and Baseline platelet count (≤ 200 × 10^9/L versus > 200 × 10^9/L) reported in the Electronic Data Capture (EDC) system.

Comparison groups	Placebo for Navitoclax + Ruxolitinib v Navitoclax + Ruxolitinib
Number of subjects included in analysis	182
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3311 [7]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Response Rate Difference
Point estimate	7.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.16
upper limit	21.24

Notes:

[7] - Navitoclax + Ruxolitinib - Placebo for Navitoclax + Ruxolitinib

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All-cause mortality/adverse events tables include events reported from time of informed consent to end of the study. Median time on follow-up: 35.5 months for Placebo for Navitoclax + Ruxolitinib group and 35.8 months for Navitoclax + Ruxolitinib group.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	27.1

Reporting groups

Reporting group title	Placebo for Navitoclax + Ruxolitinib

Reporting group description:

Placebo for navitoclax tablets were administered orally once daily (QD) per Baseline platelet count (>150 × 10^9/L starting dose of 200 mg; ≤150 × 10^9/L starting dose of 100 mg, which could be increased to 200 mg QD after 7 days provided platelet count is ≥75 × 10^9/L). Placebo for navitoclax didn't exceed 200 mg QD for first 24 weeks of treatment. After Week 25, Day 1 visit, placebo for navitoclax dose may be increased to 300 mg QD at Investigator's discretion for those with suboptimal spleen response defined as failure to achieve spleen volume reduction of at least 10% per imaging. Ruxolitinib tablets were administered orally twice daily (BID) per Baseline platelet count (>200 × 10^9/L starting dose of 20 mg; 100-200 × 10^9/L starting dose of 15 mg). Participants will continue their treatment until end of clinical benefit, unacceptable toxicity, or they meet other protocol criteria for discontinuation (whichever occurs first).

Reporting group title	Navitoclax + Ruxolitinib

Reporting group description:

Navitoclax tablets were administered orally once daily (QD) per Baseline platelet count (>150 × 10^9/L starting dose of 200 mg; ≤150 × 10^9/L starting dose of 100 mg, which could be increased to 200 mg QD after 7 days provided platelet count is ≥75 × 10^9/L). Navitoclax didn't exceed 200 mg QD for first 24 weeks of treatment. After Week 25, Day 1 visit, navitoclax dose may be increased to 300 mg QD at Investigator's discretion for those with suboptimal spleen response defined as failure to achieve spleen volume reduction of at least 10% per imaging. Ruxolitinib tablets were administered orally twice daily (BID) per Baseline platelet count (>200 × 10^9/L starting dose of 20 mg; 100-200 × 10^9/L starting dose of 15 mg). Participants will continue their treatment until end of clinical benefit, unacceptable toxicity, or they meet other protocol criteria for discontinuation (whichever occurs first).

Serious adverse events	Placebo for Navitoclax + Ruxolitinib	Navitoclax + Ruxolitinib	
Total subjects affected by serious adverse events			
subjects affected / exposed	56 / 127 (44.09%)	42 / 125 (33.60%)	
number of deaths (all causes)	28	35	
number of deaths resulting from adverse events	9	10	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
DIFFUSE LARGE B-CELL LYMPHOMA			
subjects affected / exposed	1 / 127 (0.79%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ACUTE MYELOID LEUKAEMIA			

subjects affected / exposed	1 / 127 (0.79%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
BLADDER NEOPLASM			
subjects affected / exposed	0 / 127 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
MYELOFIBROSIS			
subjects affected / exposed	2 / 127 (1.57%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
METASTATIC NEOPLASM			
subjects affected / exposed	1 / 127 (0.79%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
LYMPHOPROLIFERATIVE DISORDER			
subjects affected / exposed	0 / 127 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEPATOCELLULAR CARCINOMA			
subjects affected / exposed	1 / 127 (0.79%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
DIFFUSE LARGE B-CELL LYMPHOMA STAGE III			
subjects affected / exposed	0 / 127 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
NON-SMALL CELL LUNG CANCER			
subjects affected / exposed	0 / 127 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
SQUAMOUS CELL CARCINOMA OF SKIN			

subjects affected / exposed	0 / 127 (0.00%)	2 / 125 (1.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
TRANSFORMATION TO ACUTE MYELOID LEUKAEMIA			
subjects affected / exposed	0 / 127 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
HYPERTENSION			
subjects affected / exposed	0 / 127 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
EXTREMITY NECROSIS			
subjects affected / exposed	0 / 127 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
AORTIC STENOSIS			
subjects affected / exposed	1 / 127 (0.79%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
FINGER AMPUTATION			
subjects affected / exposed	0 / 127 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
PAIN			
subjects affected / exposed	0 / 127 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MULTIPLE ORGAN DYSFUNCTION SYNDROME			

subjects affected / exposed	0 / 127 (0.00%)	3 / 125 (2.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
GENERAL PHYSICAL HEALTH DETERIORATION			
subjects affected / exposed	2 / 127 (1.57%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEATH			
subjects affected / exposed	0 / 127 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Immune system disorders			
CYTOKINE RELEASE SYNDROME			
subjects affected / exposed	1 / 127 (0.79%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
PROSTATITIS			
subjects affected / exposed	1 / 127 (0.79%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
RESPIRATORY FAILURE			
subjects affected / exposed	1 / 127 (0.79%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
PULMONARY OEDEMA			
subjects affected / exposed	0 / 127 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PULMONARY EMBOLISM			

subjects affected / exposed	1 / 127 (0.79%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
PLEURAL EFFUSION			
subjects affected / exposed	1 / 127 (0.79%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DYSPNOEA			
subjects affected / exposed	1 / 127 (0.79%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMOTHORAX			
subjects affected / exposed	1 / 127 (0.79%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
DEPRESSION			
subjects affected / exposed	1 / 127 (0.79%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CONFUSIONAL STATE			
subjects affected / exposed	0 / 127 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
HAEMOGLOBIN DECREASED			
subjects affected / exposed	1 / 127 (0.79%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PLATELET COUNT DECREASED			
subjects affected / exposed	0 / 127 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural			

complications			
ANKLE FRACTURE			
subjects affected / exposed	1 / 127 (0.79%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CERVICAL VERTEBRAL FRACTURE			
subjects affected / exposed	0 / 127 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CRANIOFACIAL FRACTURE			
subjects affected / exposed	1 / 127 (0.79%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
FEMUR FRACTURE			
subjects affected / exposed	1 / 127 (0.79%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEAD INJURY			
subjects affected / exposed	1 / 127 (0.79%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MENISCUS INJURY			
subjects affected / exposed	1 / 127 (0.79%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
POST PROCEDURAL HAEMATOMA			
subjects affected / exposed	1 / 127 (0.79%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
POST PROCEDURAL HAEMORRHAGE			
subjects affected / exposed	1 / 127 (0.79%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RIB FRACTURE			

subjects affected / exposed	0 / 127 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUBDURAL HAEMATOMA			
subjects affected / exposed	0 / 127 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SPINAL COMPRESSION FRACTURE			
subjects affected / exposed	0 / 127 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SCAPULA FRACTURE			
subjects affected / exposed	0 / 127 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ROAD TRAFFIC ACCIDENT			
subjects affected / exposed	0 / 127 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUBDURAL HAEMORRHAGE			
subjects affected / exposed	1 / 127 (0.79%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
THORACIC VERTEBRAL FRACTURE			
subjects affected / exposed	0 / 127 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
TRANSFUSION REACTION			
subjects affected / exposed	0 / 127 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SPLENIC RUPTURE			

subjects affected / exposed	0 / 127 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
MYOCARDIAL INFARCTION			
subjects affected / exposed	0 / 127 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
EXTRASYSTOLES			
subjects affected / exposed	1 / 127 (0.79%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIO-RESPIRATORY ARREST			
subjects affected / exposed	1 / 127 (0.79%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
ATRIAL FLUTTER			
subjects affected / exposed	1 / 127 (0.79%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PALPITATIONS			
subjects affected / exposed	1 / 127 (0.79%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ACUTE MYOCARDIAL INFARCTION			
subjects affected / exposed	1 / 127 (0.79%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MYOCARDIAL ISCHAEMIA			
subjects affected / exposed	1 / 127 (0.79%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ATRIAL FIBRILLATION			

subjects affected / exposed	0 / 127 (0.00%)	2 / 125 (1.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
VENTRICULAR TACHYCARDIA			
subjects affected / exposed	0 / 127 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nervous system disorders			
TRANSIENT ISCHAEMIC ATTACK			
subjects affected / exposed	0 / 127 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SYNCOPE			
subjects affected / exposed	1 / 127 (0.79%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUBARACHNOID HAEMORRHAGE			
subjects affected / exposed	0 / 127 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
STATUS EPILEPTICUS			
subjects affected / exposed	1 / 127 (0.79%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MYASTHENIC SYNDROME			
subjects affected / exposed	1 / 127 (0.79%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEADACHE			
subjects affected / exposed	1 / 127 (0.79%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CEREBRAL INFARCTION			

subjects affected / exposed	1 / 127 (0.79%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	3 / 127 (2.36%)	3 / 125 (2.40%)	
occurrences causally related to treatment / all	2 / 3	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
THROMBOCYTOPENIA			
subjects affected / exposed	1 / 127 (0.79%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEUTROPENIA			
subjects affected / exposed	0 / 127 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DISSEMINATED INTRAVASCULAR COAGULATION			
subjects affected / exposed	0 / 127 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
RETINAL ARTERY OCCLUSION			
subjects affected / exposed	1 / 127 (0.79%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
INTESTINAL INFARCTION			
subjects affected / exposed	1 / 127 (0.79%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
GASTROOESOPHAGEAL REFLUX DISEASE			

subjects affected / exposed	1 / 127 (0.79%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROINTESTINAL OBSTRUCTION			
subjects affected / exposed	1 / 127 (0.79%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROINTESTINAL HAEMORRHAGE			
subjects affected / exposed	1 / 127 (0.79%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIARRHOEA			
subjects affected / exposed	0 / 127 (0.00%)	2 / 125 (1.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
CONSTIPATION			
subjects affected / exposed	1 / 127 (0.79%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COLITIS			
subjects affected / exposed	0 / 127 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ASCITES			
subjects affected / exposed	1 / 127 (0.79%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ABDOMINAL PAIN			
subjects affected / exposed	1 / 127 (0.79%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
OESOPHAGEAL HAEMORRHAGE			

subjects affected / exposed	1 / 127 (0.79%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
STRANGULATED UMBILICAL HERNIA			
subjects affected / exposed	1 / 127 (0.79%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
OESOPHAGEAL VARICES HAEMORRHAGE			
subjects affected / exposed	1 / 127 (0.79%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
CHOLECYSTITIS			
subjects affected / exposed	1 / 127 (0.79%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHOLECYSTITIS ACUTE			
subjects affected / exposed	0 / 127 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
ANGIOEDEMA			
subjects affected / exposed	1 / 127 (0.79%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
ACUTE KIDNEY INJURY			
subjects affected / exposed	3 / 127 (2.36%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
INTERVERTEBRAL DISC PROTRUSION			

subjects affected / exposed	0 / 127 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MUSCULAR WEAKNESS			
subjects affected / exposed	0 / 127 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
OSTEOARTHRITIS			
subjects affected / exposed	1 / 127 (0.79%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SPINAL OSTEOARTHRITIS			
subjects affected / exposed	1 / 127 (0.79%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
PNEUMONIA BACTERIAL			
subjects affected / exposed	0 / 127 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ABDOMINAL SEPSIS			
subjects affected / exposed	1 / 127 (0.79%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
APPENDICITIS			
subjects affected / exposed	1 / 127 (0.79%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CANDIDA PNEUMONIA			
subjects affected / exposed	0 / 127 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
CELLULITIS			

subjects affected / exposed	1 / 127 (0.79%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CLOSTRIDIUM COLITIS			
subjects affected / exposed	0 / 127 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	6 / 127 (4.72%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 7	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
COVID-19 PNEUMONIA			
subjects affected / exposed	3 / 127 (2.36%)	3 / 125 (2.40%)	
occurrences causally related to treatment / all	1 / 3	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
CYSTITIS BACTERIAL			
subjects affected / exposed	1 / 127 (0.79%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA			
subjects affected / exposed	5 / 127 (3.94%)	6 / 125 (4.80%)	
occurrences causally related to treatment / all	1 / 5	3 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
LOWER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	1 / 127 (0.79%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROENTERITIS BACTERIAL			
subjects affected / exposed	0 / 127 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ESCHERICHIA URINARY TRACT INFECTION			

subjects affected / exposed	0 / 127 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ESCHERICHIA SEPSIS			
subjects affected / exposed	0 / 127 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIVERTICULITIS			
subjects affected / exposed	2 / 127 (1.57%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA LEGIONELLA			
subjects affected / exposed	1 / 127 (0.79%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA RESPIRATORY SYNCYTIAL VIRAL			
subjects affected / exposed	1 / 127 (0.79%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA STAPHYLOCOCCAL			
subjects affected / exposed	0 / 127 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
PNEUMONIA STREPTOCOCCAL			
subjects affected / exposed	0 / 127 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
RESPIRATORY TRACT INFECTION VIRAL			
subjects affected / exposed	1 / 127 (0.79%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SEPSIS			

subjects affected / exposed	1 / 127 (0.79%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
TRACHEOBRONCHITIS			
subjects affected / exposed	0 / 127 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
TUBERCULOSIS			
subjects affected / exposed	0 / 127 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINARY TRACT INFECTION			
subjects affected / exposed	1 / 127 (0.79%)	2 / 125 (1.60%)	
occurrences causally related to treatment / all	1 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
UROSEPSIS			
subjects affected / exposed	1 / 127 (0.79%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
HYPERKALAEMIA			
subjects affected / exposed	0 / 127 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
TUMOUR LYSIS SYNDROME			
subjects affected / exposed	1 / 127 (0.79%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo for Navitoclax + Ruxolitinib	Navitoclax + Ruxolitinib	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	115 / 127 (90.55%)	121 / 125 (96.80%)	
Investigations			
WEIGHT INCREASED			
subjects affected / exposed	7 / 127 (5.51%)	7 / 125 (5.60%)	
occurrences (all)	12	15	
PLATELET COUNT DECREASED			
subjects affected / exposed	22 / 127 (17.32%)	33 / 125 (26.40%)	
occurrences (all)	36	90	
NEUTROPHIL COUNT DECREASED			
subjects affected / exposed	5 / 127 (3.94%)	18 / 125 (14.40%)	
occurrences (all)	7	59	
BLOOD CREATININE INCREASED			
subjects affected / exposed	7 / 127 (5.51%)	5 / 125 (4.00%)	
occurrences (all)	7	5	
BLOOD BILIRUBIN INCREASED			
subjects affected / exposed	4 / 127 (3.15%)	9 / 125 (7.20%)	
occurrences (all)	5	14	
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	12 / 127 (9.45%)	26 / 125 (20.80%)	
occurrences (all)	16	36	
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	16 / 127 (12.60%)	24 / 125 (19.20%)	
occurrences (all)	21	31	
Injury, poisoning and procedural complications			
FALL			
subjects affected / exposed	9 / 127 (7.09%)	5 / 125 (4.00%)	
occurrences (all)	11	7	
CONTUSION			
subjects affected / exposed	9 / 127 (7.09%)	14 / 125 (11.20%)	
occurrences (all)	11	18	
Vascular disorders			

HYPERTENSION			
subjects affected / exposed	11 / 127 (8.66%)	1 / 125 (0.80%)	
occurrences (all)	13	1	
Nervous system disorders			
HEADACHE			
subjects affected / exposed	11 / 127 (8.66%)	21 / 125 (16.80%)	
occurrences (all)	15	24	
PARAESTHESIA			
subjects affected / exposed	2 / 127 (1.57%)	7 / 125 (5.60%)	
occurrences (all)	2	9	
DIZZINESS			
subjects affected / exposed	12 / 127 (9.45%)	17 / 125 (13.60%)	
occurrences (all)	14	20	
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	64 / 127 (50.39%)	81 / 125 (64.80%)	
occurrences (all)	129	124	
LEUKOPENIA			
subjects affected / exposed	4 / 127 (3.15%)	8 / 125 (6.40%)	
occurrences (all)	6	11	
NEUTROPENIA			
subjects affected / exposed	10 / 127 (7.87%)	38 / 125 (30.40%)	
occurrences (all)	22	92	
THROMBOCYTOPENIA			
subjects affected / exposed	47 / 127 (37.01%)	83 / 125 (66.40%)	
occurrences (all)	108	250	
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	11 / 127 (8.66%)	8 / 125 (6.40%)	
occurrences (all)	13	12	
FATIGUE			
subjects affected / exposed	18 / 127 (14.17%)	21 / 125 (16.80%)	
occurrences (all)	20	28	
OEDEMA PERIPHERAL			
subjects affected / exposed	11 / 127 (8.66%)	13 / 125 (10.40%)	
occurrences (all)	11	13	

PYREXIA			
subjects affected / exposed	14 / 127 (11.02%)	12 / 125 (9.60%)	
occurrences (all)	22	18	
Gastrointestinal disorders			
CONSTIPATION			
subjects affected / exposed	16 / 127 (12.60%)	6 / 125 (4.80%)	
occurrences (all)	20	9	
ABDOMINAL PAIN			
subjects affected / exposed	10 / 127 (7.87%)	15 / 125 (12.00%)	
occurrences (all)	12	20	
ABDOMINAL PAIN UPPER			
subjects affected / exposed	12 / 127 (9.45%)	11 / 125 (8.80%)	
occurrences (all)	13	17	
ABDOMINAL DISTENSION			
subjects affected / exposed	4 / 127 (3.15%)	8 / 125 (6.40%)	
occurrences (all)	5	8	
NAUSEA			
subjects affected / exposed	9 / 127 (7.09%)	22 / 125 (17.60%)	
occurrences (all)	13	27	
DIARRHOEA			
subjects affected / exposed	21 / 127 (16.54%)	50 / 125 (40.00%)	
occurrences (all)	30	99	
VOMITING			
subjects affected / exposed	10 / 127 (7.87%)	12 / 125 (9.60%)	
occurrences (all)	14	14	
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	9 / 127 (7.09%)	13 / 125 (10.40%)	
occurrences (all)	10	15	
DYSPNOEA			
subjects affected / exposed	19 / 127 (14.96%)	10 / 125 (8.00%)	
occurrences (all)	20	12	
EPISTAXIS			
subjects affected / exposed	7 / 127 (5.51%)	11 / 125 (8.80%)	
occurrences (all)	7	14	
Skin and subcutaneous tissue disorders			

NIGHT SWEATS			
subjects affected / exposed	2 / 127 (1.57%)	8 / 125 (6.40%)	
occurrences (all)	2	11	
PRURITUS			
subjects affected / exposed	8 / 127 (6.30%)	14 / 125 (11.20%)	
occurrences (all)	8	19	
Musculoskeletal and connective tissue disorders			
PAIN IN EXTREMITY			
subjects affected / exposed	9 / 127 (7.09%)	5 / 125 (4.00%)	
occurrences (all)	9	6	
MUSCLE SPASMS			
subjects affected / exposed	11 / 127 (8.66%)	3 / 125 (2.40%)	
occurrences (all)	11	4	
BONE PAIN			
subjects affected / exposed	6 / 127 (4.72%)	11 / 125 (8.80%)	
occurrences (all)	6	15	
BACK PAIN			
subjects affected / exposed	13 / 127 (10.24%)	12 / 125 (9.60%)	
occurrences (all)	15	17	
ARTHRALGIA			
subjects affected / exposed	12 / 127 (9.45%)	11 / 125 (8.80%)	
occurrences (all)	13	17	
Infections and infestations			
COVID-19			
subjects affected / exposed	23 / 127 (18.11%)	31 / 125 (24.80%)	
occurrences (all)	24	33	
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	5 / 127 (3.94%)	10 / 125 (8.00%)	
occurrences (all)	7	10	
URINARY TRACT INFECTION			
subjects affected / exposed	7 / 127 (5.51%)	10 / 125 (8.00%)	
occurrences (all)	14	22	
HERPES ZOSTER			
subjects affected / exposed	6 / 127 (4.72%)	8 / 125 (6.40%)	
occurrences (all)	6	8	
Metabolism and nutrition disorders			

HYPOKALAEMIA			
subjects affected / exposed	2 / 127 (1.57%)	9 / 125 (7.20%)	
occurrences (all)	2	11	
HYPOCALCAEMIA			
subjects affected / exposed	7 / 127 (5.51%)	6 / 125 (4.80%)	
occurrences (all)	7	6	
HYPERURICAEMIA			
subjects affected / exposed	6 / 127 (4.72%)	12 / 125 (9.60%)	
occurrences (all)	6	12	
DECREASED APPETITE			
subjects affected / exposed	5 / 127 (3.94%)	7 / 125 (5.60%)	
occurrences (all)	6	8	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 June 2020	Protocol Version 2.0 Efficacy endpoints were updated. The study design was amended to double-blind with placebo to match navitoclax. Subjects classified as intermediate-1 by DIPSS+ were excluded from the study. Optional lead-in phase was added. Dose adjustment guidelines were updated per ruxolitinib label. Updated dose adjustment guidelines for thrombocytopenia for platelet counts ≥ 100 x 10^9 /L to < 125 x 10^9 /L and counts ≥ 75 x 10^9 /L to < 100 x 10^9 /L.
05 November 2020	Protocol Version 3.0 Clarification of endpoints was added. PK sampling was updated. Eligibility criteria were clarified for subjects ineligible for stem cell transplantation, subjects with an undetectable viral load, and subjects with serologic evidence of prior vaccination to HBV. Added additional hematologic samples. Statistical analyses were updated to add definition of secondary endpoints, handling of missing data, and sequence of testing for key secondary endpoints. Additional text was added to clarify that the investigator may adjust the starting dose of ruxolitinib as medically appropriate after consultation with the TA MD/SD with subsequent increase in dose as directed in the protocol. Prohibited/cautionary medications and therapy was updated regarding disulfiram, hydroxyurea, JAK inhibitors, treatments with interferon, erythropoietin, danazol, and steroids and clarified the local approved ruxolitinib product label should be referenced when coadministering with CYP3A inducers or drugs transported by P-glycoprotein and BCRP, for monitoring and dose adjustment for all hematological and non-hematological toxicities, and for dose adjustment of subjects with hepatic or renal impairment. Updated toxicity management to clarify the local approved product label for ruxolitinib should be referenced for monitoring and dose adjustment guidelines for all hematological and non-hematological toxicities in addition to the dose modification guidelines provided. Updated dose adjustment guidelines for thrombocytopenia for platelet counts ≥ 125 x 10^9 /L. Clarification was added that the study will be monitored by an IDMC.
27 May 2021	Protocol Version 4.0 Intermediate dose levels for navitoclax were added. MRI contraindication of severe anxiety and claustrophobia was added and CT scans were allowed. Ferritin was added to clinical laboratory tests. TB test at screening was clarified. Toxicity management taper verbiage was added for subjects who are at increased risk of exacerbation of splenomegaly and other significant symptoms. CT scan was allowed for MRI contraindication of severe anxiety and claustrophobia. Updated toxicity management taper verbiage for subjects who are at increased risk for exacerbation of splenomegaly and other significant symptoms. With abrupt interruption of ruxolitinib, exacerbation of disease is reported in the literature. This will enable gradual taper and interruption to minimize the risk and address the investigators' concern. Added intermediate dose levels for navitoclax. These are incorporated in this protocol for consistency across the clinical studies to minimize significant dose reductions, dose interruptions and enable appropriate dosing for subjects who experience thrombocytopenia.

03 February 2022	Protocol Version 5.0 Additional clarification on the interpretation of subject ineligible for stem cell transplantation in eligibility criteria was provided. PROs procedure on Week 1 Day 1 was clarified. Rescreening of screen-failed subjects was clarified. Updated navitoclax dose adjustment to no change or increase dose for platelet counts ≥ 125 x 10^9 /L to align with dose adjustment instructions. Navitoclax/placebo dose adjustment was aligned throughout the protocol.
31 March 2022	Protocol Version 6.0 Requirement on completing and the score calculation for MFSAF was clarified. Navitoclax/placebo dose adjustment guidelines was updated for thrombocytopenia and neutropenia to clarify action for navitoclax/placebo. MFSAF TSS calculation and symptom response assessment were updated.
23 March 2023	Protocol Version 7.0 Secondary and exploratory efficacy endpoints were updated. Continuation of study treatment for subjects with disease progression and relapse was clarified. Stratification factors were clarified.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported