Clinical trial results:
A Phase 3, Multi-Center, Randomized, Double-Blind, Placebo-Controlled Study of Fostamatinib Disodium in the Treatment of Warm Antibody Autoimmune Hemolytic Anemia

Summary

EudraCT number	2018-004774-97
Trial protocol	GB BG ES CZ HU DK DE AT BE NL IT RO
Global end of trial date	11 April 2022

Results information

Result version number	v1 (current)
This version publication date	12 May 2023
First version publication date	12 May 2023

Trial information

Trial identification

Sponsor protocol code	C-935788-057

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03764618
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Rigel Pharmaceuticals, Inc.
Sponsor organisation address	611 Gateway Blvd., South San Francisco, United States, CA 94080
Public contact	Asif Siddiqui, MS Vice President, Regulatory Affairs and Quality, Rigel Pharmaceuticals, Inc., asiddiqui@rigel.com
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Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	17 January 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 April 2022
Global end of trial reached?	Yes
Global end of trial date	11 April 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to compare the proportion of subjects with warm antibody autoimmune hemolytic anemia (wAIHA) who achieved a durable hemoglobin (Hgb) response between the fostamatinib and placebo groups.

Protection of trial subjects:

The study was conducted in accordance with Good Clinical Practice (GCP) and the Declaration of Helsinki.

Background therapy: -

Evidence for comparator:

Placebo tablets were provided to match the appearance of fostamatinib 100 mg and 150 mg tablets. Similar to fostamatinib, placebo was administered orally bid using the same escalation scheme as noted for the fostamatinib tablets.

Actual start date of recruitment	23 April 2019
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	Netherlands: 1
Country: Number of subjects enrolled	Norway: 1
Country: Number of subjects enrolled	United States: 18
Country: Number of subjects enrolled	Spain: 5
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	Austria: 6
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Bulgaria: 15
Country: Number of subjects enrolled	Czechia: 6
Country: Number of subjects enrolled	Australia: 4
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	Germany: 6
Country: Number of subjects enrolled	Georgia: 3
Country: Number of subjects enrolled	Italy: 4
Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	Ukraine: 4
Country: Number of subjects enrolled	Russian Federation: 5
Country: Number of subjects enrolled	Serbia: 2

Country: Number of subjects enrolled	Belarus: 2
Worldwide total number of subjects	90
EEA total number of subjects	49

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)	52
From 65 to 84 years	36
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

A total of 90 subjects were enrolled and treated: 45 subjects randomized to the fostamatinib group and 45 randomized to the placebo group. 18 subjects discontinued early from the study.
Subjects were recruited is US/Canada/Australia, Western Europe and Eastern Europe.

Pre-assignment

Screening details:

Male and female subjects who had a diagnosis of primary or secondary wAIHA as documented by a positive direct antiglobulin test (DAT) specific for anti-immunoglobulin G (IgG) or anti-immunoglobulin A (IgA) were were randomized in a 1:1 ratio to 1 of 2 treatment groups: fostamatinib 100 mg by mouth (PO) twice daily (bid), or matching placebo.

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, Monitor, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	A (Placebo)

Arm description:

Matching Placebo 100 mg PO, twice daily. Starting at week 4, matching Placebo 150 mg PO, twice daily, for subjects who adequately tolerated the study drug in the Investigator’s judgment.

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

Dosage and administration details:

Matching Placebo 100 mg PO, twice daily. Starting at week 4, matching Placebo 150 mg PO, twice daily, for subjects who adequately tolerated the study drug in the Investigator’s judgment.
Subjects self-administered one tablet twice daily by mouth: once in the morning and once in the evening, at least 8 hours apart, throughout the 24-week treatment period.

Arm title	B (Fostamatinib)

Arm description:

Fostamatinib 100 mg PO, twice daily. Starting at week 4, Fostamatinib 150 mg PO, twice daily, for subjects who adequately tolerated the study drug in the Investigator’s judgment.

Arm type	Experimental
Investigational medicinal product name	fostamatinib disodium
Investigational medicinal product code	R935788
Other name	R788, fostamatinib
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Fostamatinib 100 mg PO, twice daily. Starting at week 4, fostamatinib 150 mg PO, twice daily, for subjects who adequately tolerated the study drug in the Investigator’s judgment.
Subjects self-administered one tablet twice daily by mouth: once in the morning and once in the evening, at least 8 hours apart, throughout the 24-week treatment period.

Number of subjects in period 1	A (Placebo)	B (Fostamatinib)
Started	45	45
Completed	34	38
Not completed	11	7
Adverse event, serious fatal	3	2
Consent withdrawn by subject	2	1
Physician decision	-	1
Adverse event, non-fatal	3	2
Lack of efficacy	3	1

Baseline characteristics

Reporting groups	
Reporting group title	A (Placebo)
Reporting group description:	
Matching Placebo 100 mg PO, twice daily. Starting at week 4, matching Placebo 150 mg PO, twice daily, for subjects who adequately tolerated the study drug in the Investigator's judgment.	
Reporting group title	B (Fostamatinib)
Reporting group description:	
Fostamatinib 100 mg PO, twice daily. Starting at week 4, Fostamatinib 150 mg PO, twice daily, for subjects who adequately tolerated the study drug in the Investigator's judgment.	

Reporting group values	A (Placebo)	B (Fostamatinib)	Total
Number of subjects	45	45	90
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	59.9	56.8	
standard deviation	± 15.70	± 15.30	-
Gender categorical Units: Subjects			
Female	27	28	55
Male	18	17	35
Race Units: Subjects			
White	43	38	81
Black or African American	0	1	1
Asian	0	2	2
Other	1	1	2
Missing	1	3	4
Ethnicity Units: Subjects			
Not Hispanic or Latino	40	40	80
Hispanic or Latino	3	2	5
Missing	2	3	5
Concomitant Steroid Use at Baseline Units: Subjects			
< 20 mg daily	32	30	62
≥ 20 mg daily	13	15	28
Screening Hemoglobin Level Units: Subjects			
< 9 g/dL	30	30	60
≥ 9 g/dL	15	15	30
Height Units: cm			
arithmetic mean	167.77	166.57	
standard deviation	± 9.172	± 9.311	-

Weight			
Units: kg			
arithmetic mean	79.99	78.90	
standard deviation	± 14.403	± 14.410	-

End points

End points reporting groups

Reporting group title	A (Placebo)
Reporting group description:	
Matching Placebo 100 mg PO, twice daily. Starting at week 4, matching Placebo 150 mg PO, twice daily, for subjects who adequately tolerated the study drug in the Investigator's judgment.	
Reporting group title	B (Fostamatinib)
Reporting group description:	
Fostamatinib 100 mg PO, twice daily. Starting at week 4, Fostamatinib 150 mg PO, twice daily, for subjects who adequately tolerated the study drug in the Investigator's judgment.	

Primary: Achievement of durable Hgb response

End point title	Achievement of durable Hgb response
End point description:	
The primary efficacy endpoint is achievement of durable hemoglobin response (Yes/No) defined as achieving a hemoglobin level ≥ 10 g/dL with an increase from Baseline in hemoglobin level of ≥ 2 g/dL on 3 consecutive available visits during the 24-week treatment period, in which hemoglobin measurements eligible for this definition occurred outside a Rescue Treatment Visit Exclusion Period	
End point type	Primary
End point timeframe:	
From Baseline to Week 24	

End point values	A (Placebo)	B (Fostamatinib)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	45		
Units: percentage of participants				
number (confidence interval 95%)	26.7 (14.6 to 41.9)	35.6 (21.9 to 51.2)		

Statistical analyses

Statistical analysis title	Cochran-Mantel-Haenszel Test
Comparison groups	A (Placebo) v B (Fostamatinib)
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.398
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.48

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	3.66

Secondary: Hemoglobin response on at Least One Visit

End point title	Hemoglobin response on at Least One Visit
End point description:	
From Baseline to Week 24	
End point type	Secondary
End point timeframe:	
Hemoglobin response (≥ 10 mg/dL and ≥ 2 g/dL) on at Least One Visit Outside of the Rescue Treatment Exclusion Period	

End point values	A (Placebo)	B (Fostamatinib)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	45		
Units: percentage of participants				
number (confidence interval 95%)	35.6 (21.9 to 51.2)	46.7 (31.7 to 62.1)		

Statistical analyses

Statistical analysis title	Cochran-Mantel-Haenszel Test
Comparison groups	A (Placebo) v B (Fostamatinib)
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3151
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	3.68

Secondary: Achievement of a change from Baseline in the Hgb level of ≥ 2 g/dL

End point title	Achievement of a change from Baseline in the Hgb level of ≥ 2

	g/dL

End point description:

End point type	Secondary

End point timeframe:

From baseline to Week 24

End point values	A (Placebo)	B (Fostamatinib)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	45		
Units: percentage of participants				
number (confidence interval 95%)	35.6 (21.9 to 51.2)	48.9 (33.7 to 64.2)		

Statistical analyses

Statistical analysis title	Cochran-Mantel-Haenszel Test
Comparison groups	A (Placebo) v B (Fostamatinib)
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2239
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.73
upper limit	4.04

Secondary: Change in the Hgb value from Baseline to End of Treatment (Week 14 to Week 24)

End point title	Change in the Hgb value from Baseline to End of Treatment (Week 14 to Week 24)

End point description:

End point type	Secondary

End point timeframe:

From Baseline to End of Treatment (Week 14 - Week 24)

End point values	A (Placebo)	B (Fostamatinib)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	32		
Units: g/dL				
arithmetic mean (inter-quartile range (Q1-Q3))	1.99 (-0.10 to 4.33)	1.99 (0.36 to 3.51)		

Statistical analyses

Statistical analysis title	ANOVA
Comparison groups	A (Placebo) v B (Fostamatinib)
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9249
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.06
upper limit	0.96

Secondary: Use of permitted rescue medications after Week 4

End point title	Use of permitted rescue medications after Week 4

End point description:

End point type	Secondary

End point timeframe:

From Week 4 to Week 24

End point values	A (Placebo)	B (Fostamatinib)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	45		
Units: percentage of participants				
number (confidence interval 95%)	40.0 (25.7 to 55.7)	40.0 (25.7 to 55.7)		

Statistical analyses

Statistical analysis title	Cochran-Mantel-Haenszel Test
Comparison groups	A (Placebo) v B (Fostamatinib)
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.43
upper limit	2.31

Secondary: Change from Baseline to Week 24 in FACIT-F Scale

End point title	Change from Baseline to Week 24 in FACIT-F Scale
End point description:	
End point type	Secondary
End point timeframe:	
From Baseline to Week 24	

End point values	A (Placebo)	B (Fostamatinib)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	39		
Units: FACIT-F score				
arithmetic mean (inter-quartile range (Q1-Q3))	2.2 (-4.0 to 11.0)	4.1 (-3.0 to 12.0)		

Statistical analyses

Statistical analysis title	Mixed Effect Model for Repeated Measures
Comparison groups	A (Placebo) v B (Fostamatinib)
Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6963
Method	Mixed models analysis
Parameter estimate	LS mean
Point estimate	2.9

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	6.5

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From ICF signature (or the first informed consent form if more than one informed consent is signed due to rescreening) up to the final study (follow-up) visit for AEs and until 14 days of the last dose of study drug for SAEs.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups

Reporting group title	Fostamatinib

Reporting group description:

Fostamatinib 100 mg PO, twice daily. Starting at week 4, Fostamatinib 150 mg PO, twice daily, for subjects who adequately tolerated the study drug in the Investigator's judgment.

Reporting group title	Placebo

Reporting group description:

Matching Placebo 100 mg PO, twice daily. Starting at week 4, matching Placebo 150 mg PO, twice daily, for subjects who adequately tolerated the study drug in the Investigator's judgment.

Serious adverse events	Fostamatinib	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 45 (33.33%)	17 / 45 (37.78%)	
number of deaths (all causes)	2	3	
number of deaths resulting from adverse events	2	3	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoglobin decreased			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test increased			
subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			

subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Foot fracture			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	1 / 45 (2.22%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Warm type haemolytic anaemia			
subjects affected / exposed	6 / 45 (13.33%)	6 / 45 (13.33%)	
occurrences causally related to treatment / all	0 / 6	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anemia			

subjects affected / exposed	1 / 45 (2.22%)	2 / 45 (4.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cold type hemolytic anemia			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Death			
subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnea			
subjects affected / exposed	2 / 45 (4.44%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atelectasis			

subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice			
subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Primary biliary cholangitis			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
COVID-19			
subjects affected / exposed	0 / 45 (0.00%)	3 / 45 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
COVID-19 pneumonia			

subjects affected / exposed	1 / 45 (2.22%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 45 (2.22%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis bacterial			
subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Infection			
subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lyme disease			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia fungal			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Fostamatinib	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	42 / 45 (93.33%)	40 / 45 (88.89%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	11 / 45 (24.44%)	8 / 45 (17.78%)	
occurrences (all)	16	9	
General disorders and administration site conditions			

Fatigue			
subjects affected / exposed	7 / 45 (15.56%)	5 / 45 (11.11%)	
occurrences (all)	10	8	
Asthenia			
subjects affected / exposed	4 / 45 (8.89%)	6 / 45 (13.33%)	
occurrences (all)	7	10	
Pyrexia			
subjects affected / exposed	6 / 45 (13.33%)	3 / 45 (6.67%)	
occurrences (all)	7	3	
Oedema peripheral			
subjects affected / exposed	3 / 45 (6.67%)	3 / 45 (6.67%)	
occurrences (all)	4	5	
Respiratory, thoracic and mediastinal disorders			
Dyspnea			
subjects affected / exposed	6 / 45 (13.33%)	5 / 45 (11.11%)	
occurrences (all)	6	10	
Cough			
subjects affected / exposed	3 / 45 (6.67%)	1 / 45 (2.22%)	
occurrences (all)	5	1	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 45 (2.22%)	3 / 45 (6.67%)	
occurrences (all)	2	3	
Investigations			
Hemoglobin decreased			
subjects affected / exposed	8 / 45 (17.78%)	6 / 45 (13.33%)	
occurrences (all)	15	9	
Blood pressure increased			
subjects affected / exposed	4 / 45 (8.89%)	1 / 45 (2.22%)	
occurrences (all)	4	1	
Alanine aminotransferase increased			
subjects affected / exposed	3 / 45 (6.67%)	1 / 45 (2.22%)	
occurrences (all)	6	1	
Blood bilirubin increased			
subjects affected / exposed	1 / 45 (2.22%)	3 / 45 (6.67%)	
occurrences (all)	1	4	

Cardiac disorders			
Palpitations			
subjects affected / exposed	3 / 45 (6.67%)	1 / 45 (2.22%)	
occurrences (all)	3	1	
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 45 (4.44%)	5 / 45 (11.11%)	
occurrences (all)	2	7	
Headache			
subjects affected / exposed	3 / 45 (6.67%)	4 / 45 (8.89%)	
occurrences (all)	3	5	
Blood and lymphatic system disorders			
Warm type haemolytic anaemia			
subjects affected / exposed	16 / 45 (35.56%)	14 / 45 (31.11%)	
occurrences (all)	20	19	
Anemia			
subjects affected / exposed	4 / 45 (8.89%)	5 / 45 (11.11%)	
occurrences (all)	5	8	
Neutropenia			
subjects affected / exposed	3 / 45 (6.67%)	0 / 45 (0.00%)	
occurrences (all)	8	0	
Gastrointestinal disorders			
Diarrhea			
subjects affected / exposed	12 / 45 (26.67%)	3 / 45 (6.67%)	
occurrences (all)	19	4	
Nausea			
subjects affected / exposed	6 / 45 (13.33%)	4 / 45 (8.89%)	
occurrences (all)	6	5	
Abdominal pain upper			
subjects affected / exposed	1 / 45 (2.22%)	3 / 45 (6.67%)	
occurrences (all)	1	3	
Dyspepsia			
subjects affected / exposed	3 / 45 (6.67%)	0 / 45 (0.00%)	
occurrences (all)	3	0	
Hepatobiliary disorders			
Jaundice			

subjects affected / exposed	0 / 45 (0.00%)	7 / 45 (15.56%)	
occurrences (all)	0	9	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 45 (4.44%)	5 / 45 (11.11%)	
occurrences (all)	4	5	
Back pain			
subjects affected / exposed	3 / 45 (6.67%)	2 / 45 (4.44%)	
occurrences (all)	3	4	
Muscle spasms			
subjects affected / exposed	3 / 45 (6.67%)	2 / 45 (4.44%)	
occurrences (all)	4	3	
Pain in extremity			
subjects affected / exposed	1 / 45 (2.22%)	4 / 45 (8.89%)	
occurrences (all)	3	4	
Infections and infestations			
COVID-19			
subjects affected / exposed	5 / 45 (11.11%)	5 / 45 (11.11%)	
occurrences (all)	5	5	
Urinary tract infection			
subjects affected / exposed	4 / 45 (8.89%)	3 / 45 (6.67%)	
occurrences (all)	5	3	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 45 (2.22%)	3 / 45 (6.67%)	
occurrences (all)	1	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 February 2019	• Stratification criteria modified from steroid use at baseline yes/no to steroid use at baseline <20 mg and ≥ 20 mg and baseline Hgb from < 8 g/dL and ≥ 8 g/dL to < 9 g/dL and ≥ 9 g/dL • Concurrent wAIHA therapies were modified to optimize recruitment with minimal impact on confounding the efficacy endpoints including adding table for allowed concurrent therapies, adding erythropoiesis-stimulating agents (ESA), mycophenolate mofetil, dapsone, and danazol as allowed concurrent steroid therapies. Additionally, dexamethasone added but only as a rescue treatment • Allowance added for steroid taper due to input from wAIHA experts to retain subjects for the full 24-week treatment period • Changes to the primary efficacy endpoint included changing the endpoint to proportion of subjects who achieved a durable response rather than a durable hemoglobin response where a hemoglobin response was defined as a hemoglobin level of > 10 g/dL and ≥ 2 g/dL higher than the baseline (Day 1) value if, during the previous 4 weeks, the steroid dose was maintained at the baseline dose level, and rescue medication was not administered and a durable response was defined as a hemoglobin response on at least 3 scheduled visits during the 24-week evaluation period • Changes to secondary efficacy endpoints included removing average frequency of rescue AIHA regimens used, revising average number of hemoglobin assessments exhibiting a hemoglobin response to average number of weeks with hemoglobin responses, and adding proportion of subjects requiring wAIHA rescue therapy • Inclusion criteria #2, #3, #5, #8 and exclusion criteria #6 revised • Exclusion criteria #9, #11 added • Revised washout AIHA therapies table • Removed interim analysis • Follow-up period updated from Week 28 to Week 26 • Serum pregnancy tests were removed from all study visits to be collected only at screening and baseline visits, and then monthly during the study • Changing AE and SAE reporting periods

15 May 2019	• Number of weeks required to be at a stable dose prior to randomization for steroids changed from 3 weeks to 2 weeks • Steroid taper protocol revised such that there would be an option to taper steroid dose to as low as 10 mg/day (rather than 20). • Safety endpoints added including incidence of AEs, incidence of abnormal changes from baseline in laboratory values per CTCAE criteria Version 5.0 (e.g., hematology, chemistry), and incidence of changes in blood pressure compared to baseline • Inclusion criteria #2 revised to include documented positive DAT specific for anti-IgA in addition anti-IgG • Exclusion criteria #6 added exclusion for active HIV infection for patient safety • Statement about washout AIHA therapies removed and replaced with statement such that disallowed AIHA therapies are those that may not be taken within the indicated interval prior to Day 1. Ibrutinib or other BTK inhibitor added to list within 4 weeks prior to Day 1 • Analysis methods for primary efficacy endpoint revised from Pearson-chi-square test to compare the proportion of responders between the 2 treatment groups to Cochran-Mantel-Haenszel test adjusting for randomization stratification factors per advice of HA • Section on potential benefit-risk added based on prior studies per advice of HA • Section for justification of study design added per advice of HA • Section for treatment blinding and unblinding added to provide detailed information about the process of treatment unblinding, unblinding, and how the treatment group is assigned per advice of HA • Screening haptoglobin assessment added • Clarification added to allowed AIHA therapies section such that subjects requiring any AIHA therapies other than those that are allowed will be withdrawn from the study • Statement added for reporting of SUSARs in accordance with regulatory requirements • Planned analyses revised to add statement that all analysis were to be performed at a one-sided significance level of 0.025
18 May 2020	• Primary objective revised from "assess the efficacy of fostamatinib in subjects wAIHA" to "compare the proportion subjects with durable hemoglobin response between fostamatinib and placebo in subjects with wAIHA" • Secondary objectives added including to compare the proportion of subjects with hemoglobin response between the fostamatinib and placebo groups, to compare the proportion of subjects with a chain from baseline hemoglobin level of ≥ 2 g/dL between the fostamatinib and placebo groups, to compare the proportion of subjects requiring AIHA rescue therapy between the fostamatinib and placebo groups, and to compare the change in hemoglobin over time between the fostamatinib and placebo groups • Several additional efficacy and pharmacoeconomic objectives and endpoints added to support the primary endpoint including comparing the fostamatinib and placebo groups for the following endpoints: any hemoglobin level > 10 g/dL within the 24 weeks of treatment (yes/no), any change from baseline hemoglobin level ≥ 1.5 g/dL within the 24 weeks of treatment, total duration of hemoglobin response (months), time to first hemoglobin response (days), change from baseline of the total daily dose of steroids (prednisone equivalent) within the 24 weeks of treatment, change in reticulocyte count, LDH, and haptoglobin over time, change from baseline to Week 24 in FACIT-F, EQ-5D-5L at baseline and Week 24, change from baseline to Week 24 in EQ-AS, and hospitalization related to a IHA within 24 weeks of treatment (yes/no) • Similarly, secondary efficacy endpoints were revised • Safety endpoints revised • Sample size revised from 80 to 90 subjects (approximately 45 subjects per treatment group). Justification for sample size revised • Promacta added to list of allowed therapies if given as a concurrent medication and dose is stable for 4 weeks prior to randomization. Dexamethasone added as well dose was stable for 2 weeks prior to randomization

30 June 2020	• Description of procedures for blood pressure collection revised to clarify subject should rest 5 minutes before the initial measurements are collected and 3 minutes between measurements. • Added statement for clarity that subjects requiring any AIHA therapies other than those allowed, or an escalation of the allowed medications other than steroids, would be withdrawn from the study. • Guidance for restarting study drug after dose interruptions added such that Restarting study drug after interruption may require performance of procedures for safety that were missed during the interruption. The Medical Monitor should be consulted when considering study drug restart after a prolonged interruption (e.g., > 2 weeks). • Added statement in source documentation requirements that the Sponsor shall maintain the records for a period of 25 years (previously state only in country-specific amendment for Canada). • Appendix 7 added to provide guidance to Investigators on management of subjects during a pandemic.
05 March 2021	• In general, changes from Protocol V4.1 to V5.0 reflected updates to align the protocol with the revised Statistical Analysis Plan (SAP) V0.2 (dated 13 October 2020) reviewed by Health Authorities including revision of the primary efficacy endpoint, secondary efficacy endpoints, safety endpoints, and additional efficacy and pharmacoeconomic endpoints. • Added statement to section on safety monitoring to cross-reference the Investigator's brochure for guidance regarding infections and bone investigations (previously in country-specific amendment for France) • Planned analysis methods for enrollment exceptions and deviations and concomitant therapies added in accordance with the revised SAP. Examples of major deviations include subjects enrolled who do not meet eligibility criteria, subject use of non-permitted rescue medications, improper collection of or failure to collect initial study informed consent, subject receiving treatment contrary to their randomization assignment, and subject who developed withdrawal criteria during the study but were not withdrawn. • Section added for treatment compliance such that subject compliance with the assigned treatment will not be collected in the EDC system. The assessment of compliance will be based on site monitoring and pharmacy drug dispensation logs. All pharmacy logs will be kept in the trial master file. • Added laboratory tests for monocytes • Appendix 7 – Modified the number of extra bottles that can be sent to subjects during pandemic from 2 to 1

04 February 2022	• Secondary objectives and secondary efficacy endpoints were revised to include comparison of change in hemoglobin value from baseline to end of treatment (EOT) and change from baseline to Week 24 in Fatigue scale (FACIT-F) (both objectives moved up from additional efficacy objectives to secondary). A description of the FACIT-F scale added • Demographics and Baseline Characteristics will be summarized in ITT not Safety or Efficacy populations • Revised methodology to be consistent with revised objectives and endpoints for extent of exposure, laboratory values, and deaths • Additional efficacy and pharmacoeconomic objectives revised to include time to first rescue medication • Safety endpoint of TEAEs of Interest added to monitor the safety signal for AEs of interest • Statement added to treatment blinding and unblinding such that the subjects, investigators, all other site personnel, and the Sponsor/Representative will remain blinded until all subjects complete the 24 weeks of evaluation or discontinue from the study • The end of study language revised for clarification such that the end of the study occurred when the last subject had completed either the Week 24 visit or their last follow-up study visit, whichever was later • Analysis of primary efficacy endpoint revised where the study will be considered to have met its primary efficacy objective if the lower bound of the 95% CI of odds ratio of durable hemoglobin response between the fostamatinib and placebo treated subjects was >1 • Sensitivity analyses for primary endpoint added including analyses based on subgroup prognostics, multiple imputation for missing data, and a washout period of 6 weeks for rescue treatment exclusion period (rather than 4 weeks) • Methodology for analysis of secondary efficacy endpoints revised • Adjustment for multiple testing revised from rejective Bonferroni method to a hierarchical approach to control the overall Type I error for the study

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported