Clinical trial results:
A Phase 3 Open Label Extension Study of Fostamatinib Disodium in the Treatment of Persistent/Chronic Immune Thrombocytopenic Purpura (ITP).

Summary

EudraCT number	2013-005454-30
Trial protocol	GB IT HU CZ AT NL DK ES PL BG
Global end of trial date	02 June 2020

Results information

Result version number	v1 (current)
This version publication date	08 July 2021
First version publication date	08 July 2021

Trial information

Trial identification

Sponsor protocol code	0C-935788-049

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02077192
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Rigel Pharmaceuticals, Inc.
Sponsor organisation address	1180 Veterans Blvd, South San Francisco, United States, 94080
Public contact	Medical Information, Rigel Pharmaceuticals, Inc., +1 1-800-983-1329 , producthelp@rigel.com
Scientific contact	Medical Information, Rigel Pharmaceuticals, Inc., +1 1-800-983-1329 , producthelp@rigel.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	02 June 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	02 June 2020
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 assess the long term safety of fostamatinib in subjects with persistent/chronic ITP

Protection of trial subjects:

The study was conducted in accordance with Good Clinical Practices (GCP) as outlined in the International Conference on Harmonization (ICH), and the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 October 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	Norway: 2
Country: Number of subjects enrolled	Poland: 34
Country: Number of subjects enrolled	Romania: 1
Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	United Kingdom: 18
Country: Number of subjects enrolled	Austria: 1
Country: Number of subjects enrolled	Bulgaria: 12
Country: Number of subjects enrolled	Czechia: 10
Country: Number of subjects enrolled	Denmark: 1
Country: Number of subjects enrolled	Hungary: 2
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	United States: 17
Country: Number of subjects enrolled	Australia: 10
Country: Number of subjects enrolled	Canada: 4
Worldwide total number of subjects	123
EEA total number of subjects	74

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)	95
From 65 to 84 years	26
85 years and over	2

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 124 subjects were screened from studies C788-047/ C788-048 for this extension study. Out of which, 123 subjects were enrolled and treated with study drug.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Fostamitinib Disodium

Arm description:

Fostamatinib was self-administered twice daily (bid) by orally, once in the morning and once in the evening for up to 5 years or until commercial availability of fostamatinib for all subjects, whichever occurred first, in 2 dosage strengths: 100 milligram (mg) and 150 mg.

Arm type	Experimental
Investigational medicinal product name	Fostamatinib Disodium 100 mg
Investigational medicinal product code	R935788
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received Fostamatinib disodium 100 mg orally, twice daily (bid) (based on response to treatment in Study C-935788-047 or C-935788-048) for 5 years. Starting at Month 1, subjects receiving fostamatinib 100 mg bid had their dose escalated to fostamatinib disodium 150 mg bid if platelet count was less than (<) 50,000 per microliter (/mcL).

Investigational medicinal product name	Fostamatinib Disodium 150 mg
Investigational medicinal product code	R935788
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received Fostamatinib disodium 150 mg orally, bid (based on response to treatment in Study C-935788-047 or C-935788-048) for 5 years. Starting at Month 1, subjects receiving fostamatinib 100 mg bid had their dose escalated to fostamatinib 150 mg bid if platelet count was < 50,000 per mcL.

Number of subjects in period 1	Fostamitinib Disodium
Started	123
Completed	29
Not completed	94
Consent withdrawn by subject	11
Withdrew at Week 12/later due to lack of response	44

Physician decision	1
Subject was uncooperative or noncompliant to study	2
Development of study-specific AE - Withdrawal	11
Adverse event, non-fatal	10
Withdrew before Week 12 due to lack of response	9
Sponsor decision	6

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study

Reporting group description:

Baseline characteristics are analyzed with treated population data analysis set which was defined as all enrolled and treated subjects.

Reporting group values	Overall Study	Total	
Number of subjects	123	123	
Age categorical Units: Subjects			
Adults (18-64 years)	95	95	
From 65 to 84 years	26	26	
85 years and over	2	2	
Age continuous Units: years			
median	52.0		
full range (min-max)	20 to 88	-	
Gender categorical Units: Subjects			
Female	74	74	
Male	49	49	

End points

End points reporting groups

Reporting group title	Fostamitinib Disodium

Reporting group description:

Fostamatinib was self-administered twice daily (bid) by orally, once in the morning and once in the evening for up to 5 years or until commercial availability of fostamatinib for all subjects, whichever occurred first, in 2 dosage strengths: 100 milligram (mg) and 150 mg.

Primary: Percentage of Subjects who Achieved Platelet Count of at least 50,000/MicroLiter (mcL) Within 12 Weeks of Beginning Treatment up to 12 Months (Fostamatinib in 047/048 or 049):Version 1

End point title	Percentage of Subjects who Achieved Platelet Count of at least 50,000/MicroLiter (mcL) Within 12 Weeks of Beginning Treatment up to 12 Months (Fostamatinib in 047/048 or 049):Version 1[1]

End point description:

Percentage of subjects who achieved platelet count of at least 50,000/mcL within 12 Weeks of beginning treatment up to 12 months was analyzed among all subjects who received active treatment in one of the prior studies (C788-047 or C788-048), in the current extension study (C788-049), or in both prior and current studies. Treated Population was defined as all enrolled and treated subjects.

End point type	Primary

End point timeframe:

Up to 12 Months

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be reported for this endpoint.

End point values	Fostamitinib Disodium			
Subject group type	Reporting group			
Number of subjects analysed	123			
Units: Percentage of Subjects				
number (confidence interval 95%)	15.4 (9.6 to 23.1)			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects who Achieved Platelet Count of at least 50,000/mcL Within 12 Weeks of Beginning Treatment up to 12 Months (Placebo in 047/048 and Fostamatinib 049): Version 2

End point title	Percentage of Subjects who Achieved Platelet Count of at least 50,000/mcL Within 12 Weeks of Beginning Treatment up to 12 Months (Placebo in 047/048 and Fostamatinib 049): Version 2[2]

End point description:

A within-subject, between-study comparison of platelet counts for subjects who were previously treated with placebo in one of the prior studies (C788-047 or C788-048) was prospectively defined in the

protocol (version 2). Achievement of platelet response by 12 weeks and maintenance of platelet response for 12 weeks was analyzed among subjects who had been randomized to placebo in one of the prior studies (C788-047 or C788-048). Treated Population was defined as all enrolled and treated subjects.

End point type	Primary

End point timeframe:

Up to 12 Months

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be reported for this endpoint.

End point values	Fostamitinib Disodium			
Subject group type	Reporting group			
Number of subjects analysed	123			
Units: Percentage of Subjects				
number (confidence interval 95%)	2.3 (0.1 to 12.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Platelet Response Based on Platelet Count

End point title	Duration of Platelet Response Based on Platelet Count

End point description:

The duration of platelet response was defined as the time from when the subject first achieved a platelet count of at least 50,000/microliter (mcL), until the first of 2 visits with platelet counts < 50,000/mcL that were at least 4 weeks apart without an intervening visit with a platelet count less than equal to (>=) 50,000/mcL unrelated to rescue therapy. Duration of platelet response was analyzed using the Kaplan-Meier method. Treated Population was defined as all enrolled and treated subjects. Here, a number of subjects analyzed included all subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Up to 12 Months

End point values	Fostamitinib Disodium			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: Days				
median (confidence interval 95%)	127.0 (71.0 to 483.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects in Whom a Reduction in the Dose of Concomitant ITP Therapy can be Achieved While Maintaining an Adequate Platelet Count

End point title	Percentage of Subjects in Whom a Reduction in the Dose of Concomitant ITP Therapy can be Achieved While Maintaining an Adequate Platelet Count

End point description:

The percentage of subjects in whom a reduction in the dose of concomitant ITP therapy could be achieved while maintaining an adequate platelet count, the reduction event was clarified to apply only to reductions in the dose of concomitant ITP therapy occurring within a period of platelet response and the reduction event was not be prompted by an adverse event.

End point type	Secondary

End point timeframe:

Up to 12 Months

End point values	Fostamitinib Disodium			
Subject group type	Reporting group			
Number of subjects analysed	123			
Units: percentage of subjects				
number (not applicable)	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to 62 months

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Fostamitinib Disodium

Reporting group description:

Fostamatinib was self-administered twice daily (bid) by orally, once in the morning and once in the evening for up to 5 years or until commercial availability of fostamatinib for all subjects, whichever occurred first, in 2 dosage strengths: 100 milligram (mg) and 150 mg.

Serious adverse events	Fostamitinib Disodium		
Total subjects affected by serious adverse events			
subjects affected / exposed	34 / 123 (27.64%)		
number of deaths (all causes)	4		
number of deaths resulting from adverse events			
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Mucosal haemorrhage			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			

subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Menorrhagia			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	3 / 123 (2.44%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Investigations			
Transaminases increased			
subjects affected / exposed	2 / 123 (1.63%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Muscle rupture			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thoracic vertebral fracture			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac failure congestive			

subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardio-respiratory arrest			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Loss of consciousness			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	8 / 123 (6.50%)		
occurrences causally related to treatment / all	0 / 8		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Gastrointestinal haemorrhage			
subjects affected / exposed	2 / 123 (1.63%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Ascites			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Gastric antral vascular ectasia			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haemorrhoids			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haematochezia			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Melaena			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Mouth haemorrhage			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rectal haemorrhage			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Petechiae			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Purpura			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Chondrocalcinosis pyrophosphate			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Sepsis			
subjects affected / exposed	2 / 123 (1.63%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Cellulitis staphylococcal			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endocarditis bacterial			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Erythema induratum			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			

subjects affected / exposed	1 / 123 (0.81%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Mastoiditis				
subjects affected / exposed	1 / 123 (0.81%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Oral candidiasis				
subjects affected / exposed	1 / 123 (0.81%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	1 / 123 (0.81%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tuberculosis				
subjects affected / exposed	1 / 123 (0.81%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Upper respiratory tract infection				
subjects affected / exposed	1 / 123 (0.81%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	1 / 123 (0.81%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urosepsis				
subjects affected / exposed	1 / 123 (0.81%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Viral infection				

subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Fostamitinib Disodium		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	98 / 123 (79.67%)		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	12 / 123 (9.76%)		
occurrences (all)	23		
Vascular disorders			
Hypertension			
subjects affected / exposed	22 / 123 (17.89%)		
occurrences (all)	32		
Nervous system disorders			
Headache			
subjects affected / exposed	14 / 123 (11.38%)		
occurrences (all)	25		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	10 / 123 (8.13%)		
occurrences (all)	11		
Pyrexia			
subjects affected / exposed	6 / 123 (4.88%)		
occurrences (all)	12		
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	3 / 123 (2.44%)		
occurrences (all)	4		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	36 / 123 (29.27%)		
occurrences (all)	61		

Vomiting subjects affected / exposed occurrences (all)	11 / 123 (8.94%) 14		
Respiratory, thoracic and mediastinal disorders Epistaxis subjects affected / exposed occurrences (all)	17 / 123 (13.82%) 24		
Skin and subcutaneous tissue disorders Petechiae subjects affected / exposed occurrences (all)	18 / 123 (14.63%) 30		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	8 / 123 (6.50%) 8		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all)	9 / 123 (7.32%) 14 13 / 123 (10.57%) 19		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 April 2014	Protocol version 1.0 has been amended to protocol version 2.0 and the summary of changes are as below - - The exclusion criteria updated and footnote added in the study procedures for better clarity - Subjects must be willing to sign and date an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved the informed consent form (ICF) prior to participating in any study-specific screening procedure activities. Subjects will retain their same Subject ID number as per Study C-935788-047 or C-935788-048, as applicable. - The text modified in the section of dose adjustment due to adverse events to allow for additional flexibility in study drug dose for subjects in whom the clinical benefit is shown.
21 November 2014	Protocol version 2.0 amended to protocol version 3.0 and summary of changes are as below - - Revised Protocol Synopsis to include the concurrent medications and rescue therapies for more prominence - Updated the inclusion criteria for better clarity - Added footnote for the study procedures for better clarity - Adverse event definition updated and other administrative changes were made.
08 November 2016	The protocol version 3.0 has been amended to protocol version 4.0 and changes are as below - • The planned duration of treatment for individual subjects was increased from 2 to 5 years or until commercial availability of fostamatinib, whichever occurred first. Note: Fostamatinib was approved in the US in April 2018. • The visit interval for the additional treatment period (Years 3, 4, and 5) was set at every other month (as opposed to monthly for Years 1 and 2). • The WHO bleeding scale was removed as an assessment; the bleeding assessment now uses only the Immune Thrombocytopenic Purpura Bleeding Score method. • The provision for dose adjustments in the event of an excessive platelet response was removed. • A provision was made for an abbreviated or “symptom-directed” physical examination during routine visits at the investigator’s discretion. • The requirement for assessment of immunoglobulin levels every 6 months was decreased to occur just at baseline and at the end-of -study visit. • The requirement for quality of life (QoL) assessment by 36-Item Short-Form Health Survey (SF-36) was dropped after the Month 12 visit. • The summary table of cumulative blood volumes was removed. • Various edits were made for clarification or consistency; these edits did not affect the subject treatment, tests, observations, or safety.
11 November 2019	The protocol version 4.0 amended to Protocol version 5.0, and the changes are as below - - subjects who had no other treatment options and demonstrated benefit and tolerability to fostamatinib continued to receive study treatment; only serious adverse events (SAE) for these subjects were required to be reported to the Sponsor. - modified the medical monitor contact information for SAE reporting - changed the sponsor representative and signatory for the protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported