



Clinical trial results:

A Phase 3, Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Study of Fostamatinib Disodium in the Treatment of Persistent/Chronic Immune Thrombocytopenic Purpura

Summary

EudraCT number	2013-005453-76
Trial protocol	CZ AT ES PL BG
Global end of trial date	31 August 2016

Results information

Result version number	v1 (current)
This version publication date	25 September 2021
First version publication date	25 September 2021

Trial information

Trial identification

Sponsor protocol code	C-935788-048
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02076412
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Rigel Pharmaceuticals, Inc.
Sponsor organisation address	1180 Veterans Blvd, South San Francisco, CA, United States, 94080
Public contact	Clinical trials, Rigel Pharmaceuticals, Inc., +1 650-624-1100, clinicaltrials@rigel.com
Scientific contact	Clinical trials, Rigel Pharmaceuticals, Inc., +1 650-624-1100, clinicaltrials@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	28 March 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 August 2016
Global end of trial reached?	Yes
Global end of trial date	31 August 2016
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 establish the efficacy of fostamatinib disodium (fostamatinib) as compared with placebo in achieving a stable platelet response in subjects with persistent/chronic immune thrombocytopenic purpura (ITP).

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: -

Actual start date of recruitment	09 January 2015
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	Norway: 3
Country: Number of subjects enrolled	Poland: 38
Country: Number of subjects enrolled	Romania: 2
Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	Austria: 2
Country: Number of subjects enrolled	Bulgaria: 13
Country: Number of subjects enrolled	Czechia: 11
Country: Number of subjects enrolled	Germany: 1
Worldwide total number of subjects	74
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)	61
From 65 to 84 years	13
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 107 subjects were screened, 33 subjects failed screening (primarily they did not meet inclusion criteria or did meet one or more exclusion criterion), and the remaining 74 subjects were randomized, 50 to the fostamatinib group and 24 to the placebo group (ITT population).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Fostamatinib Disodium

Arm description:

Fostamatinib Disodium tablet 100 mg or 150 mg PO bid (morning and evening) over the course of 24 weeks.

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

Dosage and administration details:

Fostamatinib Disodium tablet 100 mg or 150 mg PO bid (morning and evening) over the course of 24 weeks.

Arm title	Placebo
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Arm description:

Placebo tablet PO bid (morning and evening) over the course of 24 weeks.

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

Dosage and administration details:

Placebo tablet PO bid (morning and evening)

Number of subjects in period 1	Fostamatinib Disodium	Placebo
Started	50	24
Completed	13	2
Not completed	37	22
Consent withdrawn by subject	1	1
Physician decision	1	-
Adverse event, non-fatal	2	2
Lack of efficacy	33	19

Baseline characteristics

Reporting groups

Reporting group title	Fostamatinib Disodium
Reporting group description: Fostamatinib Disodium tablet 100 mg or 150 mg PO bid (morning and evening) over the course of 24 weeks.	
Reporting group title	Placebo
Reporting group description: Placebo tablet PO bid (morning and evening) over the course of 24 weeks.	

Reporting group values	Fostamatinib Disodium	Placebo	Total
Number of subjects	50	24	74
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
arithmetic mean	49.1	49.5	
standard deviation	± 15.2	± 16.5	-
Gender categorical Units: Subjects			
Female	31	13	44
Male	19	11	30

End points

End points reporting groups

Reporting group title	Fostamatinib Disodium
Reporting group description: Fostamatinib Disodium tablet 100 mg or 150 mg PO bid (morning and evening) over the course of 24 weeks.	
Reporting group title	Placebo
Reporting group description: Placebo tablet PO bid (morning and evening) over the course of 24 weeks.	

Primary: Number of Participants With Stable Platelet Response of at Least 50,000/ μ L

End point title	Number of Participants With Stable Platelet Response of at Least 50,000/ μ L
End point description: Stable platelet response by Week 24 defined as a platelet count of at least 50,000/ μ L on at least 4 of the 6 visits between Weeks 14-24	
End point type	Primary
End point timeframe: Baseline to Week 24	

End point values	Fostamatinib Disodium	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	24		
Units: Number of Participants With Stable Plate	9	1		

Statistical analyses

Statistical analysis title	Statistical Analysis for Primary Outcome
Comparison groups	Fostamatinib Disodium v Placebo
Number of subjects included in analysis	74
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1519
Method	Fisher exact
Parameter estimate	Risk difference (RD)
Point estimate	13.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	27.1

Secondary: Number of Participants With Platelet Count \geq 50,000/ μ L at Week 12

End point title	Number of Participants With Platelet Count \geq 50,000/ μ L at Week 12
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End point description:

Platelet Count \geq 50,000/ μ L at Week 12

End point type	Secondary
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End point timeframe:

Baseline to Week 12

End point values	Fostamatinib Disodium	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	24		
Units: Number of Participants With Platelet Cou	12	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Platelet Count \geq 50,000/ μ L at Week 24

End point title	Number of Participants With Platelet Count \geq 50,000/ μ L at Week 24
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End point description:

Platelet Count \geq 50,000/ μ L at Week 24

End point type	Secondary
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End point timeframe:

Baseline to Week 24

End point values	Fostamatinib Disodium	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	24		
Units: Number of Participants With Platelet Cou	8	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Platelet Count \geq 30,000/ μ L and at Least 20,000/ μ L Above Baseline at Week 12

End point title	Number of Participants With Platelet Count \geq 30,000/ μ L and at Least 20,000/ μ L Above Baseline at Week 12
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End point description:

Among subjects with a baseline platelet count $<$ 15,000/ μ L, achievement of a count \geq 30,000/ μ L and at least 20,000/ μ L above baseline at Week 12.

End point type	Secondary
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End point timeframe:

Baseline to Week 12

End point values	Fostamatinib Disodium	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	9		
Units: Number of Participants With Platelet Cou	6	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Platelet Count \geq 30,000/ μ L and at Least 20,000/ μ L Above Baseline at Week 24

End point title	Number of Participants With Platelet Count \geq 30,000/ μ L and at Least 20,000/ μ L Above Baseline at Week 24
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End point description:

Among subjects with a baseline platelet count $<$ 15,000/ μ L, achievement of a count \geq 30,000/ μ L and at least 20,000/ μ L above baseline at Week 24

End point type	Secondary
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End point timeframe:

Baseline to Week 24

End point values	Fostamatinib Disodium	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	9		
Units: Number of Participants With Platelet Cou	3	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Frequency and Severity of Bleeding According to the ITP Bleeding Score (IBLS)

End point title	Frequency and Severity of Bleeding According to the ITP Bleeding Score (IBLS)
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End point description:

The ITP Bleeding Scale (IBLS) is an immune thrombocytopenic purpura (ITP)-specific bleeding score used to analyze the correlation of clinical and laboratory platelet variables with bleeding. The IBLS comprises of 11 grades from 0 (none) to 2 (marked bleeding) by history over the previous week or by exam; 2 being worse. These 11 grades include: skin by physical exam, oral by physical exam, skin by history, oral by history, epistaxis, gastrointestinal, urinary, gynecological, pulmonary, intracranial hemorrhage, and subconjunctival hemorrhage. After each grade is scored, the mean value for all 11 grades is calculated (lowest score being 0 and highest score being 2) for each subject visit. LOCF method was used to impute any missing data.

The mean of the IBLS scores across visits during the 24-week treatment period was summarized by treatment group using descriptive statistics. A 2-sided, 2-sample t-test was used to test for a difference in means between treatments for this endpoint.

End point type	Secondary
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End point timeframe:

Baseline to Week 24

End point values	Fostamatinib Disodium	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	24		
Units: scores on a scale				
arithmetic mean (standard deviation)	0.04 (\pm 0.08)	0.06 (\pm 0.07)		

Statistical analyses

Statistical analysis title	Statistica Analysis for ITP Bleeding Score
Comparison groups	Placebo v Fostamatinib Disodium
Number of subjects included in analysis	74
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4927 ^[1]
Method	t-test, 2-sided
Parameter estimate	Risk difference (RD)
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.05
upper limit	0.02

Notes:

[1] - P-value from a two-sided two-sample t-test, testing for a difference in means between fostamatinib and placebo.

Secondary: Frequency and Severity of Bleeding According to the World Health Organization (WHO) Bleeding Scale

End point title	Frequency and Severity of Bleeding According to the World
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End point description:

The World Health Organization (WHO) bleeding scale is a standardized grading scale created to measure the severity of bleeding. The scale is a clinical investigator-assessed five-point scale with a score range starting at the lowest 0=No bleeding, 1 = Petechiae, 2=Mild blood loss, 3=Gross blood loss, to the worse 4=Debilitating blood loss. The WHO bleeding scale is scored by history over the previous-week or by exam. After each grade is scored, the mean value is calculated (lowest score being 0 [no bleeding] to the highest score being 4 [debilitating blood loss]) for each visit. LOCF method was used to impute any missing data.

The mean of the WHO bleeding scale across visits during the 24-week treatment period was summarized by treatment group using descriptive statistics. A 2-sided, 2-sample t-test was used to test for a difference in means between treatments for this endpoint.

End point type	Secondary
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End point timeframe:

Baseline to Week 24

End point values	Fostamatinib Disodium	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	24		
Units: scores on a scale				
arithmetic mean (standard deviation)	0.26 (± 0.38)	0.38 (± 0.47)		

Statistical analyses

Statistical analysis title	Statistica Analysis for WHO Bleeding Scale
Comparison groups	Fostamatinib Disodium v Placebo
Number of subjects included in analysis	74
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2499 ^[2]
Method	t-test, 2-sided
Parameter estimate	Risk difference (RD)
Point estimate	-0.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.32
upper limit	0.09

Notes:

[2] - P-value from a two-sided two-sample t-test, testing for a difference in means between fostamatinib and placebo.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

24 weeks

Adverse event reporting additional description:

One patient randomized to the placebo group was given the wrong treatment kit, and was treated with fostamatinib for 2 weeks. This patient's efficacy data were analyzed with the placebo arm, but his safety data were analyzed with the fostamatinib arm.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.1
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Reporting groups

Reporting group title	Fostamatinib Recipient
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Reporting group description:

Fostamatinib (100 mg PO bid or 150 mg PO bid)

Reporting group title	Placebo Recipient
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Reporting group description:

Placebo

Serious adverse events	Fostamatinib Recipient	Placebo Recipient	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 51 (9.80%)	6 / 23 (26.09%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Plasma cell myeloma			
subjects affected / exposed	1 / 51 (1.96%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Investigations			
Platelet count decreased			
subjects affected / exposed	1 / 51 (1.96%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Muscle rupture			

subjects affected / exposed	0 / 51 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			
subjects affected / exposed	1 / 51 (1.96%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertensive crisis			
subjects affected / exposed	1 / 51 (1.96%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Transient ischaemic attack			
subjects affected / exposed	1 / 51 (1.96%)	0 / 23 (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			
Thrombocytopenia			
subjects affected / exposed	0 / 51 (0.00%)	3 / 23 (13.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Menorrhagia			
subjects affected / exposed	0 / 51 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	1 / 51 (1.96%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Petechiae			

subjects affected / exposed	0 / 51 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 51 (1.96%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 51 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Fostamatinib Recipient	Placebo Recipient	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	35 / 51 (68.63%)	15 / 23 (65.22%)	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	3 / 51 (5.88%)	0 / 23 (0.00%)	
occurrences (all)	4	0	
Vascular disorders			
Hypertension			
subjects affected / exposed	7 / 51 (13.73%)	3 / 23 (13.04%)	
occurrences (all)	7	4	
Haematoma			
subjects affected / exposed	1 / 51 (1.96%)	2 / 23 (8.70%)	
occurrences (all)	1	2	
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 51 (5.88%)	3 / 23 (13.04%)	
occurrences (all)	4	6	
Gastrointestinal disorders			

Diarrhoea			
subjects affected / exposed	9 / 51 (17.65%)	3 / 23 (13.04%)	
occurrences (all)	15	3	
Nausea			
subjects affected / exposed	4 / 51 (7.84%)	3 / 23 (13.04%)	
occurrences (all)	5	3	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	6 / 51 (11.76%)	1 / 23 (4.35%)	
occurrences (all)	7	1	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	3 / 51 (5.88%)	1 / 23 (4.35%)	
occurrences (all)	3	1	
Petechiae			
subjects affected / exposed	3 / 51 (5.88%)	1 / 23 (4.35%)	
occurrences (all)	3	2	
Infections and infestations			
Bronchitis			
subjects affected / exposed	2 / 51 (3.92%)	0 / 23 (0.00%)	
occurrences (all)	2	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 April 2014	The protocol version 2.0 dated 08 April 2014 included the following main changes: <ul style="list-style-type: none">• Revision of inclusion and exclusion criteria• Addition of D-dimer testing to Visit 1• Clarification that subjects who require a washout period greater than 30 days should sign the informed consent form at a prescreening visit prior to beginning washout• Clarification that the Visit 3 SF-36 assessment would be administered after the Visit 2 assessments are complete in the event that Visit 2 and Visit 3 occur on the same day• Subjects who have a dose reduction to due adverse events may be allowed to have their dose re-escalated after the adverse event has resolved following consultation with the Medical Monitor• Removal of measurement of IgD and IgE levels.
09 December 2014	The protocol version 3.0 dated 09 December 2014 included the following main changes: <ul style="list-style-type: none">• Revision of inclusion and exclusion criteria• Revision of washout requirements to clarify that subjects must discontinue all therapeutic agents, other than those allowed as ITP concomitant therapy• Clarification that subjects may continue the specific concurrent therapies for ITP that are allowed at study entry• Definition of requirements for the withdrawal visit assessments in order to facilitate smooth transition to Study C-935788-049, if applicable• Clarification that testing for D-dimer is only required for subjects that have a history of DVT.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported