EU Clinical Trials Register

Clinical trial results:
A Phase II, Single Arm, Multicenter, Proof-of-Mechanism Study to Investigate the Safety, Tolerability, Efficacy, Pharmacokinetics, and Pharmacodynamics of Bitopertin (RO4917838) in Adults with Non Transfusion-Dependent beta-Thalassemia

Summary

EudraCT number	2016-004799-23
Trial protocol	IT
Global end of trial date	29 June 2018

Results information

Result version number	v1 (current)
This version publication date	06 July 2019
First version publication date	06 July 2019

Trial information

Trial identification

Sponsor protocol code	BP39642

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03271541
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.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 June 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 June 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This was a proof-of-mechanism study designed to investigate the safety, tolerability, efficacy, pharmacokinetics, and pharmacodynamics of multiple oral doses of bitopertin in adults with non-transfusion-dependent (NTD) beta-thalassemia.

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 October 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Italy: 2
Country: Number of subjects enrolled	Lebanon: 5
Country: Number of subjects enrolled	Thailand: 5
Worldwide total number of subjects	12
EEA total number of subjects	2

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)	12
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at three centers in Italy, Lebanon, and Thailand.

Pre-assignment

Screening details:

The study population consisted of male and female subjects between ages 18-55 (inclusive) with a confirmed diagnosis of NTD beta-thalassemia.

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	Bitopertin

Arm description:

Subjects underwent 6 weeks of dose-escalation, followed by 10 weeks of treatment at the attained target dose of bitopertin, and 6 weeks of follow-up.

Arm type	Experimental
Investigational medicinal product name	Bitopertin
Investigational medicinal product code	
Other name	RO4917838
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received once-daily oral doses of bitopertin according to the following schedule: 30mg for Days 1-14, 60mg for Days 15-28, and 90mg for days 29-42.

Number of subjects in period 1	Bitopertin
Started	12
Completed	9
Not completed	3
Physician decision	1
Study termination by sponsor	1
Lack of efficacy	1

Baseline characteristics

Reporting groups

Reporting group title	Bitopertin

Reporting group description:

Subjects underwent 6 weeks of dose-escalation, followed by 10 weeks of treatment at the attained target dose of bitopertin, and 6 weeks of follow-up.

Reporting group values	Bitopertin	Total	
Number of subjects	12	12	
Age categorical Units: Subjects			
Adults (18-64 years)	12	12	
Age continuous Units: years			
arithmetic mean	32.8		
standard deviation	± 9.7	-	
Gender categorical Units: Subjects			
Female	7	7	
Male	5	5	
Race (NIH/OMB) Units: Subjects			
Asian	5	5	
White	7	7	
Ethnicity (NIH/OMB) Units: Subjects			
Not Hispanic or Latino	12	12	

End points

End points reporting groups

Reporting group title	Bitopertin
Reporting group description:	
Subjects underwent 6 weeks of dose-escalation, followed by 10 weeks of treatment at the attained target dose of bitopertin, and 6 weeks of follow-up.	

Primary: Safety Outcome: Percentage of Participants with Adverse Events (AEs) - Part 1 only

End point title	Safety Outcome: Percentage of Participants with Adverse Events (AEs) - Part 1 only[1]
End point description:	
An adverse event is any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporarily associated with the use of a pharmaceutical product, whether or not considered related to the pharmaceutical product. Preexisting conditions which worsen during a study are also considered adverse events.	
End point type	Primary
End point timeframe:	
Baseline, Week 16, up to Week 22	
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: No formal hypothesis testing was performed.	

End point values	Bitopertin			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: Percent				
number (not applicable)	91.7			

Statistical analyses

No statistical analyses for this end point

Primary: Efficacy Outcome: Change in Total Hemoglobin (Hb) Level from Baseline to End of 16-Week Treatment Period in Part 1

End point title	Efficacy Outcome: Change in Total Hemoglobin (Hb) Level from Baseline to End of 16-Week Treatment Period in Part 1[2]
End point description:	
End point type	Primary
End point timeframe:	
Baseline to Week 16	

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: No formal hypothesis testing was performed.

End point values	Bitopertin			
Subject group type	Reporting group			
Number of subjects analysed	12[3]			
Units: g/dL				
arithmetic mean (standard deviation)				
Baseline	92.5 (± 12.5)			
Change from Baseline at Week 16	1.3 (± 6.1)			

Notes:

[3] - Data from 12 subjects was available at baseline. Six subjects were analyzed at Week 16.

Statistical analyses

No statistical analyses for this end point

Primary: Long-term Safety Outcome : Percentage of Participants with Adverse Events (AEs) - Part 2 only

End point title	Long-term Safety Outcome : Percentage of Participants with Adverse Events (AEs) - Part 2 only[4]

End point description:

An adverse event is any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporarily associated with the use of a pharmaceutical product, whether or not considered related to the pharmaceutical product. Preexisting conditions which worsen during a study are also considered adverse events.

End point type	Primary

End point timeframe:

Baseline to 19 Months

Notes:

[4] - 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: No formal hypothesis testing was performed.

End point values	Bitopertin			
Subject group type	Reporting group			
Number of subjects analysed	0[5]			
Units: None				
number (not applicable)				

Notes:

[5] - Part 2 was not conducted.

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic Concentrations of Bitopertin

End point title	Pharmacokinetic Concentrations of Bitopertin

End point description:

End point type	Secondary

End point timeframe:
Part 1: Predose (0 H) on Days 2, 15, 29, 57, 85, 113

End point values	Bitopertin			
Subject group type	Reporting group			
Number of subjects analysed	12[6]			
Units: ug/mL				
arithmetic mean (standard deviation)				
Day 2	60.0 (± 15.93)			
Day 15	152.4 (± 94.82)			
Day 29	271.6 (± 146.68)			
Day 57	373.4 (± 312.73)			
Day 85	281.2 (± 298.73)			
Day 113	190.3 (± 191.65)			

Notes:
[6] - n=12 for the first time point. For Days 15, 29, 57, 85, and 113, n=11, 12, 10, 11, and 6.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Absolute Reticulocyte Count

End point title	Change from Baseline in Absolute Reticulocyte Count

End point description:

End point type	Secondary

End point timeframe:
Part 1: Baseline, Week 16

End point values	Bitopertin			
Subject group type	Reporting group			
Number of subjects analysed	12[7]			
Units: 10^9/L				
arithmetic mean (standard deviation)				
Baseline	139.43 (± 48.17)			
Change from Baseline at Week 16	12.32 (± 27.35)			

Notes:

[7] - Data from 12 subjects was available at baseline. Six subjects were analyzed at Week 16.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Serum Lactate Dehydrogenase Level

End point title	Change from Baseline in Serum Lactate Dehydrogenase Level
End point description:	
End point type	Secondary
End point timeframe:	
Part 1: Baseline, Week 16	

End point values	Bitopertin			
Subject group type	Reporting group			
Number of subjects analysed	12[8]			
Units: U/L				
arithmetic mean (standard deviation)				
Baseline	391.7 (± 108.5)			
Change from Baseline at Week 16	-95.0 (± 93.2)			

Notes:

[8] - Data from 12 subjects was available at baseline. Six subjects were analyzed at Week 16.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Serum Bilirubin Level

End point title	Change from Baseline in Serum Bilirubin Level
End point description:	
End point type	Secondary
End point timeframe:	
Part 1: Baseline, Week 16	

End point values	Bitopertin			
Subject group type	Reporting group			
Number of subjects analysed	12[9]			
Units: umol/L				
arithmetic mean (standard deviation)				
Baseline	72.49 (± 40.41)			
Change from Baseline at Week 16	2.11 (± 32.58)			

Notes:

[9] - Data from 12 subjects was available at baseline. Six subjects were analyzed at Week 16.

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent Clearance of Bitopertin

End point title	Apparent Clearance of Bitopertin
End point description:	

End point type	Secondary
End point timeframe:	
Part 1: Predose (0 H) on Days 2, 15, 29, 57, 85, 113	

End point values	Bitopertin			
Subject group type	Reporting group			
Number of subjects analysed	0[10]			
Units: None				
number (not applicable)				

Notes:

[10] - This OM was not reported due to study termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Volume of Distribution of Bitopertin

End point title	Volume of Distribution of Bitopertin
End point description:	

End point type	Secondary
End point timeframe:	
Part 1: Predose (0 H) on Days 2, 15, 29, 57, 85, 113	

End point values	Bitopertin			
Subject group type	Reporting group			
Number of subjects analysed	0[11]			
Units: None				
number (not applicable)				

Notes:

[11] - This OM was not reported due to study termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Concentration-Time Curve (AUC) of Bitopertin within a Dosing Interval

End point title	Area Under the Concentration-Time Curve (AUC) of Bitopertin within a Dosing Interval

End point description:

End point type	Secondary

End point timeframe:

Part 1: Predose (0 H) on Days 2, 15, 29, 57, 85, 113

End point values	Bitopertin			
Subject group type	Reporting group			
Number of subjects analysed	0[12]			
Units: None				
number (not applicable)				

Notes:

[12] - This OM was not reported due to study termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Minimum Observed Concentration (Cmin) of Bitopertin

End point title	Minimum Observed Concentration (Cmin) of Bitopertin

End point description:

End point type	Secondary

End point timeframe:

Part 1: Predose (0 H) on Days 2, 15, 29, 57, 85, 113

End point values	Bitopertin			
Subject group type	Reporting group			
Number of subjects analysed	0[13]			
Units: None				
number (not applicable)				

Notes:

[13] - This OM was not reported due to study termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Concentration (Cmax) of Bitopertin

End point title	Maximum Observed Concentration (Cmax) of Bitopertin
End point description:	

End point type	Secondary
End point timeframe:	
Part 1: Predose (0 H) on Days 2, 15, 29, 57, 85, 113	

End point values	Bitopertin			
Subject group type	Reporting group			
Number of subjects analysed	0[14]			
Units: None				
number (not applicable)				

Notes:

[14] - This OM was not reported due to study termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent Elimination Half-Life of Bitopertin

End point title	Apparent Elimination Half-Life of Bitopertin
End point description:	

End point type	Secondary
End point timeframe:	
Part 1: Predose (0 H) on Days 2, 15, 29, 57, 85, 113	

End point values	Bitopertin			
Subject group type	Reporting group			
Number of subjects analysed	0[15]			
Units: None				
number (not applicable)				

Notes:

[15] - This OM was not reported due to study termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Accumulation Ratio of Bitopertin

End point title	Accumulation Ratio of Bitopertin
End point description:	
End point type	Secondary

End point timeframe:

Part 1: Predose (0 H) on Days 2, 15, 29, 57, 85, 113

End point values	Bitopertin			
Subject group type	Reporting group			
Number of subjects analysed	0[16]			
Units: None				
number (not applicable)				

Notes:

[16] - This OM was not reported due to study termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Absolute Red Blood Cell Count

End point title	Change from Baseline in Absolute Red Blood Cell Count
End point description:	
End point type	Secondary

End point timeframe:

Part 1: Baseline, Week 16.

End point values	Bitopertin			
Subject group type	Reporting group			
Number of subjects analysed	0[17]			
Units: None				
number (not applicable)				

Notes:

[17] - This OM was not reported due to study termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Total Hb Level from Baseline to the End of the Treatment Period in Part 2

End point title	Change in Total Hb Level from Baseline to the End of the Treatment Period in Part 2
End point description:	
End point type	Secondary
End point timeframe:	
Baseline, 19 Months	

End point values	Bitopertin			
Subject group type	Reporting group			
Number of subjects analysed	0[18]			
Units: None				
number (not applicable)				

Notes:

[18] - Part 2 was not conducted.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:	
Baseline through the end of study	
Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	Bitopertin

Reporting group description:

Part 1 - The main study - 16 weeks in total: Participants will undergo a 6-week dose-escalation period followed by 10 weeks of treatment at the attained target dose of bitopertin. Part 2 - Open Label Extension (OLE) - up to an additional 12 months: Participants will be given the option to enroll into the OLE once the 16-week treatment of Part 1 has been completed. Participants who decide not to enroll in the OLE, at the end of Part 1 will enter a 6-week follow-up period.

Serious adverse events	Bitopertin		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 12 (8.33%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Cardiac disorders			
Chest pain			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Biliary colic			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Abdominal pain upper			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Non-serious adverse events	Bitopertin		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 12 (91.67%)		
Investigations			
Haemoglobin decreased			
subjects affected / exposed	3 / 12 (25.00%)		
occurrences (all)	3		
Injury, poisoning and procedural complications			
Muscle strain			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Nervous system disorders			
Dizziness			
subjects affected / exposed	5 / 12 (41.67%)		
occurrences (all)	8		
Headache			
subjects affected / exposed	3 / 12 (25.00%)		
occurrences (all)	5		
Somnolence			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
General disorders and administration site conditions			
Face oedema			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	2		
Eye disorders			
Vision blurred			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Gastrointestinal disorders			
Vomiting			

subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Pruritis			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Folliculitis			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Pharyngitis			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Upper respiratory tract infection			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	3		
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Hypoglycaemia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 December 2017	Added an open-label extension; added a new dose formulation; adjustment to ophthalmological assessments

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The study was prematurely terminated, and Part 2 was not conducted.

Notes: