Clinical trial results:
A sequential, open-label, two-period study to assess the pharmacokinetics, safety and tolerability of two dose levels of AFQ056 in male, adolescent patients with Fragile X Syndrome (12 to 18 years inclusive)

Summary

EudraCT number	2010-019353-18
Trial protocol	Outside EU/EEA
Global end of trial date	29 December 2010

Results information

Result version number	v1 (current)
This version publication date	13 July 2016
First version publication date	26 July 2015

Trial information

Trial identification

Sponsor protocol code	CAFQ056B2131

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, +41 613241111,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, +41 613241111,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001003-PIP01-10
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	29 December 2010
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 December 2010
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the study was to evaluate the single-dose pharmacokinetics of mavoglurant (25 mg, 50 mg or 100 mg) capsules in male adolescent subjects (aged 12-18 years) suffering with Fragile X Syndrome (FXS).

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed. No rescue medications were permitted during the study as there are no approved treatments for FXS currently. If the investigator deemed that rescue medication for specific symptoms was necessary, the subject had to be discontinued from the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 September 2010
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	Switzerland: 12
Worldwide total number of subjects	12
EEA total number of subjects	0

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)	12
Adults (18-64 years)	0
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at single centre in Switzerland.

Pre-assignment

Screening details:

A total of 12 subjects were enrolled in the study.

Period 1

Period 1 title	First Intervention Period
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

As the current study was an open label study, this section was not applicable.

Arms

Arm title	AFQ056 25 mg

Arm description:

Subjects received one capsule of AFQ056 25 mg.

Arm type	Experimental
Investigational medicinal product name	Mavoglurant
Investigational medicinal product code	AFQ056
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

One capsule of AFQ056 25 mg was administered.

Number of subjects in period 1	AFQ056 25 mg
Started	12
Completed	11
Not completed	1
Consent withdrawn by subject	1

Period 2

Period 2 title	Second Intervention Period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

As the current study was an open label study, this section was not applicable.

Arms	
Are arms mutually exclusive?	Yes
Arm title	AFQ056 50 mg

Arm description:

Subjects received two capsules of AFQ056 25 mg.

Arm type	Experimental
Investigational medicinal product name	Mavoglurant
Investigational medicinal product code	AFQ056
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Two capsules of AFQ056 25 mg were administered.

Arm title	AFQ056 100 mg

Arm description:

Subjects received one capsule of AFQ056 100 mg.

Arm type	Experimental
Investigational medicinal product name	Mavoglurant
Investigational medicinal product code	AFQ056
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

One capsule of AFQ056 100 mg was administered.

Number of subjects in period 2	AFQ056 50 mg	AFQ056 100 mg
Started	4	7
Completed	4	7

Baseline characteristics

Reporting groups	
Reporting group title	AFQ056 25 mg
Reporting group description:	
Subjects received one capsule of AFQ056 25 mg.	

Reporting group values	AFQ056 25 mg	Total	
Number of subjects	12	12	
Age categorical Units: Subjects			
Adolescents (12- 17 years)	12	12	
Age continuous Units: years			
arithmetic mean	13.8		
standard deviation	± 1.71	-	
Gender categorical Units: Subjects			
Female	0	0	
Male	12	12	

End points

End points reporting groups

Reporting group title	AFQ056 25 mg
Reporting group description:	
Subjects received one capsule of AFQ056 25 mg.	
Reporting group title	AFQ056 50 mg
Reporting group description:	
Subjects received two capsules of AFQ056 25 mg.	
Reporting group title	AFQ056 100 mg
Reporting group description:	
Subjects received one capsule of AFQ056 100 mg.	

Primary: AUC From Time Zero to Extrapolated Infinite Time (AUCinf)

End point title	AUC From Time Zero to Extrapolated Infinite Time (AUCinf)[1]
End point description:	
AUCinf was the area under the plasma concentration versus time curve (AUC) from time zero (pre-dose) to infinity. Analysis was performed in pharmacokinetic (PK) set population which included all the subjects who received at least one dose of study drug and had data for at least one of the primary PK variables in at least one period and no major protocol deviations with impact on PK data.	
End point type	Primary
End point timeframe:	
Pre-dose (0), 1, 2.5, 4, 8, 12, 16 and 24 hours post-dose	

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 summary statistics was planned for this primary outcome measure.

End point values	AFQ056 25 mg	AFQ056 50 mg	AFQ056 100 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	11[2]	4	7	
Units: hour.nanograms/millilitre(hr.ng/mL)				
arithmetic mean (standard deviation)	364.8 (± 169.52)	871.2 (± 351.8)	1131 (± 560.28)	

Notes:

[2] - Result for one subject was excluded, since terminal phase was not evaluable.

Statistical analyses

No statistical analyses for this end point

Primary: AUC From Time Zero to Last Measurable Concentration [AUClast]

End point title	AUC From Time Zero to Last Measurable Concentration [AUClast][3]
End point description:	
Area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration. It was calculated as the sum of linear trapezoids using non-compartmental analysis. Analysis was performed in PK set population.	
End point type	Primary

End point timeframe:

Pre-dose (0), 1, 2.5, 4, 8, 12, 16 and 24 hours post-dose

Notes:

[3] - 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 summary statistics was planned for this primary outcome measure.

End point values	AFQ056 25 mg	AFQ056 50 mg	AFQ056 100 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	4	7	
Units: hr.ng/mL				
arithmetic mean (standard deviation)	357.9 (± 176.25)	790.2 (± 287.36)	1022 (± 494.89)	

Statistical analyses

No statistical analyses for this end point

Primary: Maximum Observed Plasma Concentration (Cmax)

End point title	Maximum Observed Plasma Concentration (Cmax)[4]

End point description:

Maximum observed plasma concentration following drug administration from the raw plasma concentration-time data. Analysis was performed in PK set population.

End point type	Primary

End point timeframe:

Pre-dose (0), 1, 2.5, 4, 8, 12, 16 and 24 hours post-dose

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: Only descriptive summary statistics was planned for this primary outcome measure.

End point values	AFQ056 25 mg	AFQ056 50 mg	AFQ056 100 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	4	7	
Units: ng/mL				
arithmetic mean (standard deviation)	68.01 (± 20.801)	143 (± 39.741)	185.8 (± 110.5)	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Reach Maximum Observed Plasma Concentration (Tmax)

End point title	Time to Reach Maximum Observed Plasma Concentration (Tmax)

End point description:

Tmax was defined as the time required to reach maximum observed plasma concentration. Tmax was directly determined from the raw plasma concentration-time data. Analysis was performed in PK set

population.

End point type	Secondary

End point timeframe:

Pre-dose (0), 1, 2.5, 4, 8, 12, 16 and 24 hours post-dose

End point values	AFQ056 25 mg	AFQ056 50 mg	AFQ056 100 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	4	7	
Units: Hours (hr)				
median (full range (min-max))	1 (1 to 2.75)	1 (1 to 1)	1 (0.92 to 4)	

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent Plasma Clearance (CL/F)

End point title	Apparent Plasma Clearance (CL/F)

End point description:

The apparent body clearance of drug from the plasma (CL/F) and it was calculated as Dose/AUCinf, where CL was the clearance of the drug and F was the absolute oral bioavailability. Analysis was performed in PK set population.

End point type	Secondary

End point timeframe:

Pre-dose (0), 1, 2.5, 4, 8, 12, 16 and 24 hours post-dose

End point values	AFQ056 25 mg	AFQ056 50 mg	AFQ056 100 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	11[5]	4	7	
Units: Litre/hour(L/hr)				
arithmetic mean (standard deviation)	94.1 (± 73)	65.3 (± 26.9)	111 (± 57.4)	

Notes:

[5] - Result for one subject was excluded, since terminal phase was not evaluable.

Statistical analyses

No statistical analyses for this end point

Secondary: Elimination half-life (T1/2)

End point title	Elimination half-life (T1/2)

End point description:

The elimination half-life associated with the terminal slope of a semi logarithmic concentration-time curve. Analysis was performed in PK set population.

End point type	Secondary

End point timeframe:

Pre-dose (0), 1, 2.5, 4, 8, 12, 16 and 24 hours post-dose

End point values	AFQ056 25 mg	AFQ056 50 mg	AFQ056 100 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	11[6]	4	7	
Units: Hour (hr)				
arithmetic mean (standard deviation)	6.96 (± 4.2)	6.6 (± 1.93)	7.21 (± 1.93)	

Notes:

[6] - Result for one subject was excluded, since terminal phase was not evaluable.

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent Volume of Distribution (Vz/F)

End point title	Apparent Volume of Distribution (Vz/F)

End point description:

Apparent volume of distribution was calculated by using the formula (CL/F)/λz, where CL/F was oral total plasma clearance and λz was terminal elimination rate constant. Analysis was performed in PK set population.

End point type	Secondary

End point timeframe:

Pre-dose (0), 1, 2.5, 4, 8, 12, 16 and 24 hours post-dose

End point values	AFQ056 25 mg	AFQ056 50 mg	AFQ056 100 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	11[7]	4	7	
Units: Litre (L)				
arithmetic mean (standard deviation)	713 (± 324)	599 (± 278)	1163 (± 657)	

Notes:

[7] - Result for one subject was excluded, since terminal phase was not evaluable.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with adverse events (AEs) and serious adverse events(SAEs)

End point title	Number of subjects with adverse events (AEs) and serious adverse events(SAEs)

End point description:

An AE was defined as any unfavorable and unintended sign, symptom, or disease temporally associated with the use of study drug, whether or not related to study drug. A SAE was defined as an event which

was fatal or life threatening, required or prolonged hospitalization, was significantly or permanently disabling or incapacitating, constituted a congenital anomaly or a birth defect, or encompassed any other clinically significant event that could jeopardize the subject or require medical or surgical intervention to prevent one of the aforementioned outcomes. All subjects who received at least one dose of study drug were included in the safety analysis set.

End point type	Secondary

End point timeframe:

From start of study treatment to end of study

End point values	AFQ056 25 mg	AFQ056 50 mg	AFQ056 100 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	4	7	
Units: Number of subjects				
AEs	3	0	0	
SAEs	0	0	0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All adverse events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	13.1

Reporting groups	
Reporting group title	25 mg AFQ056
Reporting group description:	
Subjects received one capsule of AFQ056 25 mg.	

Serious adverse events	25 mg AFQ056		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 12 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	25 mg AFQ056		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 12 (25.00%)		
Investigations			
Blood amylase increased			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Lipase increased			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		

Infections and infestations Nail infection subjects affected / exposed occurrences (all)	 1 / 12 (8.33%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported