Clinical trial results:
An open-label, randomized, single dose, two period, crossover study to determine the bioequivalence between valsartan 160 mg pediatric final market image (FMI) formulation (solution) and clinical service form (CSF) of valsartan 160 mg extemporaneous suspension in healthy adult volunteers.

Summary

EudraCT number	2016-004323-23
Trial protocol	Outside EU/EEA
Global end of trial date	14 August 2008

Results information

Result version number	v1 (current)
This version publication date	28 March 2018
First version publication date	28 March 2018

Trial information

Trial identification

Sponsor protocol code	CVAL489K2101

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-000005-PIP01-07
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	14 August 2008
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 August 2008
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the rate and extent of absorption of valsartan between the valsartan pediatric FMI formulation and a valsartan CSF extemporaneous suspension.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 August 2008
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	India: 86
Worldwide total number of subjects	86
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)	0
Adults (18-64 years)	86
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Each subject participated in a 21-day screening period, two baseline periods and two treatment periods and an end-of-study evaluation. The washout period between the two treatments was at least 7 days.

Period 1

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

Arms

Arm title	All Subjects

Arm description:

Treatment sequence: Valsartan pediatric FMI formulation(3mg/mL)/Valsartan CSF extemporaneous suspension(16mg/mL) followed by Valsartan CSF extemporaneous suspension (16mg/mL)/ Valsartan pediatric FMI formulation (3mg/mL).

Arm type	Experimental
Investigational medicinal product name	Valsartan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

A suspension was prepared by using marketed valsartan tablets 160 mg, commercially available suspending and sweetening agent. 53.3 ml of this solution will be administered, so that the final dose will be equivalent to 160 mg Valsartan.

Investigational medicinal product name	Ora-Plus®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for oral suspension
Routes of administration	Oral use

Dosage and administration details:

A commercial suspending vehicle.

Investigational medicinal product name	Ora-Sweet®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for oral suspension
Routes of administration	Oral use

Dosage and administration details:

A commercial sweetening vehicle.

Investigational medicinal product name	Valsartan Extemporaneous Suspension
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

A suspension was prepared by using marketed valsartan tablets 160 mg, commercially available

suspending and sweetening agent. 10 ml of this suspension was administered orally to give 160 mg Valsartan.

Number of subjects in period 1	All Subjects
Started	86
Completed	81
Not completed	5
Consent withdrawn by subject	2
Adverse event, non-fatal	2
Protocol deviation	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall Period

Reporting group description: -

Reporting group values	Overall Period	Total	
Number of subjects	86	86	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	86	86	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	28.8		
standard deviation	± 6.27	-	
Gender categorical Units: Subjects			
Female	0	0	
Male	86	86	

End points

End points reporting groups

Reporting group title	All Subjects
Reporting group description: Treatment sequence: Valsartan pediatric FMI formulation(3mg/mL)/Valsartan CSF extemporaneous suspension(16mg/mL) followed by Valsartan CSF extemporaneous suspension (16mg/mL)/ Valsartan pediatric FMI formulation (3mg/mL).	
Subject analysis set title	Treatment A - Solution formulation
Subject analysis set type	Sub-group analysis
Subject analysis set description: Valsartan pediatric FMI formulation (3 mg/mL oral solution)	
Subject analysis set title	Treatment B - Extemporaneous suspension
Subject analysis set type	Sub-group analysis
Subject analysis set description: Valsartan CSF extemporaneous suspension (16 mg/mL oral suspension)	

Primary: Cmax of Valsartan following single oral dose of 160 mg Valsartan pediatric FMI solution formulation and 160 mg valsartan CSF extemporaneous suspension

End point title	Cmax of Valsartan following single oral dose of 160 mg Valsartan pediatric FMI solution formulation and 160 mg valsartan CSF extemporaneous suspension
End point description: Maximum (peak) plasma (or blood, serum, other body fluid) drug concentration after drug administration [ng/mL]	
End point type	Primary
End point timeframe: Pre-dose, 0.25, 0.5, 1, 2 , 3, 4, 6, 8, 10, 12, 16, 24, 36 and 48 hours post - dosing following Treatment A and Treatment B.	

End point values	Treatment A - Solution formulation	Treatment B - Extemporaneous suspension		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	83[1]	83[2]		
Units: ng/mL				
arithmetic mean (standard deviation)	8655 (± 1743)	6571 (± 1519)		

Notes:

[1] - Pharmacokinetic Analysis Population

[2] - Pharmacokinetic Analysis Population

Statistical analyses

Statistical analysis title	Geometric mean ratio of Cmax
Comparison groups	Treatment A - Solution formulation v Treatment B - Extemporaneous suspension

Number of subjects included in analysis	166
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Ratio of geometric means
Point estimate	1.32
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.27
upper limit	1.38

Primary: AUC (0-t) and AUC (0-∞) of Valsartan following single oral dose of 160 mg Valsartan pediatric FMI solution formulation and 160 mg Valsartan CSF extemporaneous suspension

End point title	AUC (0-t) and AUC (0-∞) of Valsartan following single oral dose of 160 mg Valsartan pediatric FMI solution formulation and 160 mg Valsartan CSF extemporaneous suspension

End point description:

AUC(0-t) measures area under the concentration-time curve from time zero to time t, where t is the last time point with measurable concentration [h.ng/mL].
AUC(0-∞) measures area under the concentration-time curve from time zero to infinity [h.ng/mL].

End point type	Primary

End point timeframe:

Pre-dose, 0.25, 0.5, 1, 2 , 3, 4, 6, 8, 10, 12, 16, 24, 36 and 48 hours post - dosing following Treatment A and Treatment B.

End point values	Treatment A - Solution formulation	Treatment B - Extemporaneous suspension		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	82[3]	82[4]		
Units: h.ng/mL				
arithmetic mean (standard deviation)				
AUC (0-t)	52410 (± 14951)	48080 (± 14140)		
AUC (0-∞)	52910 (± 15050)	48540 (± 14240)		

Notes:

[3] - Pharmacokinetic Analysis Population

[4] - Pharmacokinetic Analysis Population

Statistical analyses

Statistical analysis title	Geometric mean ratio of AUC (0-t)
Comparison groups	Treatment B - Extemporaneous suspension v Treatment A - Solution formulation

Number of subjects included in analysis	164
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Ratio of geometric means
Point estimate	1.09
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.05
upper limit	1.13

Statistical analysis title	Geometric mean ratio of AUC (0-∞)
Comparison groups	Treatment A - Solution formulation v Treatment B - Extemporaneous suspension
Number of subjects included in analysis	164
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Ratio of geometric means
Point estimate	1.09
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.05
upper limit	1.13

Primary: Tmax of Valsartan following single oral dose of 160 mg Valsartan pediatric FMI solution formulation and 160 mg Valsartan CSF extemporaneous suspension

End point title	Tmax of Valsartan following single oral dose of 160 mg Valsartan pediatric FMI solution formulation and 160 mg Valsartan CSF extemporaneous suspension[5]

End point description:

Tmax measures time to reach peak or maximum concentration following drug administration [h].

End point type	Primary

End point timeframe:

Pre-dose, 0.25, 0.5, 1, 2 , 3, 4, 6, 8, 10, 12, 16, 24, 36 and 48 hours post - dosing following Treatment A and Treatment B.

Notes:

[5] - 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 statistical analyses have been reported for this primary end point.

End point values	Treatment A - Solution formulation	Treatment B - Extemporaneous suspension		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	83[6]	83[7]		
Units: hour				
median (full range (min-max))	1.0 (1.0 to 2.0)	3.0 (1.0 to 4.0)		

Notes:

[6] - Pharmacokinetic Analysis Population

[7] - Pharmacokinetic Analysis Population

Statistical analyses

No statistical analyses for this end point

Primary: T1/2 of Valsartan following single oral dose of 160 mg Valsartan pediatric FMI solution formulation and 160 mg Valsartan CSF extemporaneous suspension

End point title	T1/2 of Valsartan following single oral dose of 160 mg Valsartan pediatric FMI solution formulation and 160 mg Valsartan CSF extemporaneous suspension[8]

End point description:

t1/2 The elimination half-life associated with the terminal slope (λz) of a semilogarithmic concentration-time curve [h]

End point type	Primary

End point timeframe:

Pre-dose, 0.25, 0.5, 1, 2 , 3, 4, 6, 8, 10, 12, 16, 24, 36 and 48 hours post - dosing following Treatment A and Treatment B.

Notes:

[8] - 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 statistical analyses have been reported for this primary end point.

End point values	Treatment A - Solution formulation	Treatment B - Extemporaneous suspension		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	82[9]	82[10]		
Units: hour				
arithmetic mean (standard deviation)	7.6 (± 1.3)	7.6 (± 1.6)		

Notes:

[9] - Pharmacokinetic Analysis Population

[10] - Pharmacokinetic Analysis Population

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	11.0

Reporting groups

Reporting group title	Valsartan pediatric FMI formulation (3mg/mL)

Reporting group description:

Valsartan pediatric FMI formulation (3mg/mL)

Reporting group title	Valsartan CSF extemporaneous suspension (16mg/mL)

Reporting group description:

Valsartan CSF extemporaneous suspension (16mg/mL)

Reporting group title	All Subjects

Reporting group description:

All Subjects

Serious adverse events	Valsartan pediatric FMI formulation (3mg/mL)	Valsartan CSF extemporaneous suspension (16mg/mL)	All Subjects
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 85 (0.00%)	0 / 83 (0.00%)	0 / 86 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Valsartan pediatric FMI formulation (3mg/mL)	Valsartan CSF extemporaneous suspension (16mg/mL)	All Subjects
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 85 (4.71%)	1 / 83 (1.20%)	5 / 86 (5.81%)
General disorders and administration site conditions			
PYREXIA			
subjects affected / exposed	1 / 85 (1.18%)	0 / 83 (0.00%)	1 / 86 (1.16%)
occurrences (all)	1	0	1

Gastrointestinal disorders VOMITING subjects affected / exposed occurrences (all)	1 / 85 (1.18%) 1	0 / 83 (0.00%) 0	1 / 86 (1.16%) 1
Infections and infestations GASTROENTERITIS subjects affected / exposed occurrences (all)	1 / 85 (1.18%) 1	0 / 83 (0.00%) 0	1 / 86 (1.16%) 1
PHARYNGITIS subjects affected / exposed occurrences (all)	1 / 85 (1.18%) 1	1 / 83 (1.20%) 1	2 / 86 (2.33%) 2

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