Clinical trial results:
A Comparative, Randomized, Single-Dose, 2-Way Crossover Bioavailability Study of a Compounded 4 mg/mL Olmesartan Medoxomil Suspension (Total Dose 40 mg) and 40 mg Olmesartan Medoxomil Tablets (Benicar®) in Healthy Adult Volunteers Under Fasting Conditions

Summary

EudraCT number	2015-003005-41
Trial protocol	Outside EU/EEA
Global end of trial date	13 December 2004

Results information

Result version number	v1 (current)
This version publication date	20 November 2018
First version publication date	02 September 2016

Trial information

Trial identification

Sponsor protocol code	CS0866-A-U101

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Sankyo Pharma Development
Sponsor organisation address	399 Thornall Street, Edison, United States, NJ 08837
Public contact	Daiichi Sankyo Pharma Development, 399 Thornall Street, Edison, NJ 08837, United States, Jason Mann, +001 732 5905011, jamann@dsi.com
Scientific contact	Daiichi Sankyo Pharma Development, 399 Thornall Street, Edison, NJ 08837, United States, Jason Mann, +001 732 5905011, jamann@dsi.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000897-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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 December 2004
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 December 2004
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study was to determine if the compounded suspension formulation of olmesartan medoxomil (4 milligrams per milliliter [mg/mL] × 10 mL, for a total dose of 40 mg) is bioequivalent to the marketed tablet formulation of Benicar (1 × 40 mg tablet).

Protection of trial subjects:

Safety variables included clinical and laboratory adverse events, concomitant medications, physical examination findings, vital signs, electrocardiogram (ECG) results, and hematology, serum chemistry, and urinalysis laboratory results.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 October 2004
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	United States: 26
Worldwide total number of subjects	26
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)	26

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were screened from 24 October 2004 to 14 November 2004.

Pre-assignment

Screening details:

A total of 26 subjects were enrolled and randomized into the study. Of these 24 subjects completed the study.

Period 1

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

Arms

Are arms mutually exclusive?	No
Arm title	Sequence AB

Arm description:

Subjects were administered with 10 milliliter (ml) (4 milligram per milliliter [mg/ml]) olmesartan medoxomil oral suspension (Treatment A) on Day 1 of Period 1 and 40 mg of olmesartan medoxomil tablet (Benicar) (Treatment B) on Day 1 of Period 2. Both the periods were separated by a washout period of 7 days.

Arm type	Experimental
Investigational medicinal product name	Olmesartan Medoxomil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral suspension
Routes of administration	Oral use

Dosage and administration details:

Subjects were administered with olmesartan medoxomil oral suspension (Benicar 20 mg tablets dispersed in a vehicle containing water, Ora-Plus, and Ora-Sweet) on Day 1 of either Period 1 or Period 2 with 240 ml of water.

Investigational medicinal product name	Olmesartan Medoxomil
Investigational medicinal product code	
Other name	Benicar
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects were administered with 40 mg of olmesartan medoxomil tablet on Day 1 of either Period 1 or Period 2 with 240 ml of water.

Arm title	Sequence BA

Arm description:

Subjects were administered with 40 mg of olmesartan medoxomil tablet (Treatment B) on Day 1 of Period 1 and 10 mL (4 mg/mL) olmesartan medoxomil oral suspension (Treatment A) on Day 1 of Period 2. Both the periods were separated by a washout period of 7 days.

Arm type	Active comparator
Investigational medicinal product name	Olmesartan Medoxomil
Investigational medicinal product code	
Other name	Benicar
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects were administered with 40 mg of olmesartan medoxomil tablet on Day 1 of either Period 1 or Period 2 with 240 ml of water.

Investigational medicinal product name	Olmesartan Medoxomil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral suspension
Routes of administration	Oral use

Dosage and administration details:

Subjects were administered with olmesartan medoxomil oral suspension (Benicar 20 mg tablets dispersed in a vehicle containing water, Ora-Plus, and Ora-Sweet) on Day 1 of either Period 1 or Period 2 with 240 ml of water.

Number of subjects in period 1	Sequence AB	Sequence BA
Started	13	13
Completed	13	11
Not completed	0	2
Physician decision	-	1
Lost to follow-up	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Sequence AB
Reporting group description:	
Subjects were administered with 10 milliliter (ml) (4 milligram per milliliter [mg/ml]) olmesartan medoxomil oral suspension (Treatment A) on Day 1 of Period 1 and 40 mg of olmesartan medoxomil tablet (Benicar) (Treatment B) on Day 1 of Period 2. Both the periods were separated by a washout period of 7 days.	
Reporting group title	Sequence BA
Reporting group description:	
Subjects were administered with 40 mg of olmesartan medoxomil tablet (Treatment B) on Day 1 of Period 1 and 10 mL (4 mg/mL) olmesartan medoxomil oral suspension (Treatment A) on Day 1 of Period 2. Both the periods were separated by a washout period of 7 days.	

Reporting group values	Sequence AB	Sequence BA	Total
Number of subjects	13	13	26
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	13	13	26
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	2	2	4
Male	11	11	22

End points

End points reporting groups

Reporting group title	Sequence AB

Reporting group description:

Subjects were administered with 10 milliliter (ml) (4 milligram per milliliter [mg/ml]) olmesartan medoxomil oral suspension (Treatment A) on Day 1 of Period 1 and 40 mg of olmesartan medoxomil tablet (Benicar) (Treatment B) on Day 1 of Period 2. Both the periods were separated by a washout period of 7 days.

Reporting group title	Sequence BA

Reporting group description:

Subjects were administered with 40 mg of olmesartan medoxomil tablet (Treatment B) on Day 1 of Period 1 and 10 mL (4 mg/mL) olmesartan medoxomil oral suspension (Treatment A) on Day 1 of Period 2. Both the periods were separated by a washout period of 7 days.

Subject analysis set title	Treatment A
Subject analysis set type	Per protocol

Subject analysis set description:

Subjects included who were received at least one dose of 10 mL (4 mg/mL) olmesartan medoxomil oral suspension on Day 1 of either Period 1 or Period 2 with 240 ml of water.

Subject analysis set title	Treatment B
Subject analysis set type	Per protocol

Subject analysis set description:

Subjects included who were received at least one dose of 40 mg of olmesartan medoxomil tablet on Day 1 of either Period 1 or Period 2 with 240 ml of water.

Primary: Area Under the Curve From Time Zero to Last Quantifiable Concentration (AUC0-t) of Olmesartan Medoxomil

End point title	Area Under the Curve From Time Zero to Last Quantifiable Concentration (AUC0-t) of Olmesartan Medoxomil

End point description:

The AUC(0-t) is the area under the curve from time zero to last quantifiable concentration of olmesartan medoxomil. Pharmacokinetic population included all subjects who received at least one dose of study drug and had a valid Pharmacokinetic profile.

End point type	Primary

End point timeframe:

Pre-dose, and 0.25, 0.5, 0.75, 1, 1.333, 1.667, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, 36, 48 and 60 hours post-dose after each treatment period

End point values	Treatment A	Treatment B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	24	26		
Units: nanogram*hour per milliliter (ng*hr/mL)				
geometric mean (geometric coefficient of variation)	6812.6 (± 24.3)	6358.5 (± 27)		

Statistical analyses

Statistical analysis title	Statistical Analysis: AUC0-t
Statistical analysis description:	
The statistical analyses were performed using the SAS® Mixed Procedure. There were a total of 26 subjects included in this analysis (cross-over design).	
Comparison groups	Treatment A v Treatment B
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Geometric Means Ratio
Point estimate	105.2
Confidence interval	
level	90 %
sides	2-sided
lower limit	97.7
upper limit	113.3

Primary: Maximum Observed Plasma Concentration (Cmax) of Olmesartan Medoxomil

End point title	Maximum Observed Plasma Concentration (Cmax) of Olmesartan Medoxomil
End point description:	
The Cmax is the maximum observed plasma concentration of olmesartan medoxomil. Pharmacokinetic population included all subjects who received at least one dose of study drug and had a valid Pharmacokinetic profile.	
End point type	Primary
End point timeframe:	
Pre-dose, and 0.25, 0.5, 0.75, 1, 1.333, 1.667, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, 36, 48 and 60 hours post-dose after each treatment period	

End point values	Treatment A	Treatment B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	24	26		
Units: nanogram /milliliter (ng/mL)				
geometric mean (geometric coefficient of variation)	1036.9 (± 27.3)	949.6 (± 27.9)		

Statistical analyses

Statistical analysis title	Statistical Analysis: Cmax
Statistical analysis description:	
The statistical analyses were performed using the SAS® Mixed Procedure. There were a total of 26 subjects included in this analysis (cross-over design).	
Comparison groups	Treatment A v Treatment B

Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Geometric Means Ratio
Point estimate	106.6
Confidence interval	
level	90 %
sides	2-sided
lower limit	97.8
upper limit	116.3

Primary: Area Under the Concentration-time Curve From Time Zero to Infinity (AUC0-inf) of Olmesartan Medoxomil

End point title	Area Under the Concentration-time Curve From Time Zero to Infinity (AUC0-inf) of Olmesartan Medoxomil

End point description:

The AUC (0-infinity) is the area under the plasma concentration-time curve from time zero to infinite time, calculated as the sum of AUC(last) and C(last)/lambda(z); wherein AUC(last) is area under the plasma concentration-time curve from time zero to last quantifiable time, C(last) is the last observed quantifiable concentration, and lambda(z) is elimination rate constant. Pharmacokinetic population included all subjects who received at least one dose of study drug and had a valid Pharmacokinetic profile. Here 'number of subject analysed' is the number of subject analysed for this outcome measure.

End point type	Primary

End point timeframe:

Pre-dose, and 0.25, 0.5, 0.75, 1, 1.333, 1.667, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, 36, 48 and 60 hours post-dose after each treatment period

End point values	Treatment A	Treatment B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	23		
Units: nanogram*hour per milliliter (ng*hr/mL)				
geometric mean (geometric coefficient of variation)	7184.2 (± 26.6)	6594.3 (± 28)		

Statistical analyses

Statistical analysis title	Statistical Analysis: AUC0-inf

Statistical analysis description:

The statistical analyses were performed using the SAS® Mixed Procedure. There were a total of 23 subjects included in this analysis (cross-over design).

Comparison groups	Treatment A v Treatment B

Number of subjects included in analysis	43
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Geometric Means Ratio
Point estimate	107.2
Confidence interval	
level	90 %
sides	2-sided
lower limit	97.5
upper limit	117.9

Primary: Ratio of AUC0-t to AUC0-inf (AUC0-t to AUCinf) of Olmesartan Medoxomil

End point title	Ratio of AUC0-t to AUC0-inf (AUC0-t to AUCinf) of Olmesartan Medoxomil[1]

End point description:

Ratio of AUC0-t to AUC0-inf (AUC0-t to AUCinf) of olmesartan medoxomil. Here number of subject analysed' is the number of subject analysed for this outcome measure. Pharmacokinetic population included all subjects who received at least one dose of study drug and had a valid Pharmacokinetic profile.

End point type	Primary

End point timeframe:

Pre-dose, and 0.25, 0.5, 0.75, 1, 1.333, 1.667, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, 36, 48 and 60 hours post-dose after each treatment period

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: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	Treatment A	Treatment B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	23		
Units: Ratio				
arithmetic mean (standard deviation)	0.9722 (± 0.03137)	0.9745 (± 0.0219)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From the start of the study treatment up to Day 3 of Period 2 (approximately 11 days)	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	7.1
Reporting groups	
Reporting group title	Treatment A
Reporting group description:	
Subjects included who were received at least one dose of 10 mL (4 mg/mL) olmesartan medoxomil oral suspension on Day 1 of either Period 1 or Period 2 with 240 ml of water.	
Reporting group title	Treatment B
Reporting group description:	
Subjects included who were received at least one dose of 40 mg of olmesartan medoxomil tablet on Day 1 of either Period 1 or Period 2 with 240 ml of water.	

Serious adverse events	Treatment A	Treatment B	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 13 (0.00%)	0 / 11 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Treatment A	Treatment B	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 13 (15.38%)	2 / 11 (18.18%)	
Injury, poisoning and procedural complications			
Joint sprain			
subjects affected / exposed	0 / 13 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 13 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Headache			

subjects affected / exposed	1 / 13 (7.69%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Fatigue			
subjects affected / exposed	1 / 13 (7.69%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 13 (7.69%)	0 / 11 (0.00%)	
occurrences (all)	1	0	

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