

**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) | EMA-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 (\pm 24.3) | 6358.5 (\pm 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 occurrences (all) | 1 / 13 (7.69%) 1 | 0 / 11 (0.00%) 0 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 1 / 11 (9.09%) 1 | |
| Fatigue | | | |
| subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | 1 / 11 (9.09%) 1 | |
| Gastrointestinal disorders | | | |
| Nausea | | | |
| subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | 0 / 11 (0.00%) 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