



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) | EMA-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 (λ_z) 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 (\pm 1.3) | 7.6 (\pm 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 | 1 / 85 (1.18%) | 0 / 83 (0.00%) | 1 / 86 (1.16%) |
| occurrences (all) | 1 | 0 | 1 |
| Infections and infestations | | | |
| GASTROENTERITIS | | | |
| subjects affected / exposed | 1 / 85 (1.18%) | 0 / 83 (0.00%) | 1 / 86 (1.16%) |
| occurrences (all) | 1 | 0 | 1 |
| PHARYNGITIS | | | |
| subjects affected / exposed | 1 / 85 (1.18%) | 1 / 83 (1.20%) | 2 / 86 (2.33%) |
| occurrences (all) | 1 | 1 | 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