



Clinical trial results:

An Open-label, Randomized, Single-dose, 2-Period, 2-Treatment Crossover Study to Assess the Bioequivalence of Cinacalcet Capsule (Administered as Six of the 5-mg Cinacalcet Capsules) With 30-mg Commercial Cinacalcet Tablet in Healthy Adult Volunteers

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2017-002659-28 |
| Trial protocol | Outside EU/EEA |
| Global end of trial date | 28 December 2016 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 30 December 2017 |
| First version publication date | 30 December 2017 |

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | 20160428 |
|-----------------------|----------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Amgen |
| Sponsor organisation address | One Amgen Center Drive, Thousand Oaks, CA, United States, 91320 |
| Public contact | IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.com |
| Scientific contact | IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.com |

Notes:

Paediatric regulatory details

| | |
|--|---------------------|
| Is trial part of an agreed paediatric investigation plan (PIP) | Yes |
| EMA paediatric investigation plan number(s) | EMA-000078-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 | 28 December 2016 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 28 December 2016 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the bioequivalence, based on the area under the plasma drug concentration-time curve from time zero to infinity (AUCinf), area under the plasma drug concentration-time curve from time zero to a specific time point (AUC0-t), and the maximum observed concentration (Cmax), between the contents of six of the 5-mg cinacalcet capsules sprinkled over applesauce and a single 30-mg commercial formulation tablet of cinacalcet with applesauce in healthy adult volunteers.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) and applicable national and regional regulations/guidelines. The protocol, proposed informed consent form, other written subject information, and any proposed advertising material were reviewed and approved by an institutional review board (IRB) before recruitment of subjects into the study and shipment of Amgen investigational product to the study site. The investigator obtained written informed consent from the subject or legally acceptable representative after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any investigational product was administered.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 07 December 2016 |
| 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: 44 |
| Worldwide total number of subjects | 44 |
| 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 | 0 |

| | |
|---------------------------|----|
| months) | |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 44 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

This study was conducted at a single site in the United States.

Pre-assignment

Screening details:

Healthy men and women who were 18 to 65 years of age (inclusive) at the time of randomization were eligible for participation in this 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

| | |
|-----------|------------|
| Arm title | Cinacalcet |
|-----------|------------|

Arm description:

Participants received Treatment A (contents of six 5-mg capsules of cinacalcet sprinkled over 4 oz of applesauce), and Treatment B (a single 30-mg tablet of cinacalcet with 4 oz of applesauce) in 1 of 2 sequences: AB or BA, separated by a washout period of at least 7 days.

| | |
|--|-----------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Cinacalcet Tablet |
| Investigational medicinal product code | |
| Other name | Sensipar® Mimpara® |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

A single 30-mg oral dose of cinacalcet given as one 30-mg tablet swallowed whole with 240 mL of water following consumption of 4 oz of applesauce. The applesauce was consumed within 1 minute and dosing occurred within 1 minute of finishing the applesauce.

| | |
|--|-----------------------|
| Investigational medicinal product name | Cinacalcet Capsules |
| Investigational medicinal product code | |
| Other name | Sensipar® Mimpara® |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

A single 30-mg oral dose of cinacalcet given as the contents of six 5-mg capsules sprinkled over 4 oz of applesauce and consumed within 1 minute with 240 mL of water.

| Number of subjects in period 1 | Cinacalcet |
|--------------------------------|------------|
| Started | 44 |
| Completed | 43 |
| Not completed | 1 |
| Decision by Sponsor | 1 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|---------------|
| Reporting group title | Overall Study |
|-----------------------|---------------|

Reporting group description:

Participants received Treatment A (contents of six 5-mg capsules of cinacalcet sprinkled over 4 oz of applesauce), and Treatment B (a single 30-mg tablet of cinacalcet with 4 oz of applesauce) in 1 of 2 sequences: AB or BA, separated by a washout period of at least 7 days.

| Reporting group values | Overall Study | Total | |
|---|---------------|-------|--|
| Number of subjects | 44 | 44 | |
| Age Categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 44 | 44 | |
| From 65-84 years | 0 | 0 | |
| 85 years and over | 0 | 0 | |
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | 38.1 | | |
| standard deviation | ± 9.5 | - | |
| Gender Categorical | | | |
| Units: Subjects | | | |
| Female | 4 | 4 | |
| Male | 40 | 40 | |
| Race | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 2 | 2 | |
| Asian | 2 | 2 | |
| Black or African American | 12 | 12 | |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | |
| White | 27 | 27 | |
| Other | 1 | 1 | |
| Ethnicity | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 19 | 19 | |
| Not Hispanic or Latino | 25 | 25 | |

End points

End points reporting groups

| | |
|---|--------------------------|
| Reporting group title | Cinacalcet |
| Reporting group description: Participants received Treatment A (contents of six 5-mg capsules of cinacalcet sprinkled over 4 oz of applesauce), and Treatment B (a single 30-mg tablet of cinacalcet with 4 oz of applesauce) in 1 of 2 sequences: AB or BA, separated by a washout period of at least 7 days. | |
| Subject analysis set title | Cinacalcet 30 mg Capsule |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Participants received a single 30-mg oral dose of cinacalcet given as the contents of six 5-mg capsules sprinkled over 4 oz of applesauce and consumed within 1 minute with 240 mL of water | |
| Subject analysis set title | Cinacalcet 30 mg Tablet |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Participants received a single 30-mg oral dose of cinacalcet given as one 30-mg tablet swallowed whole with 240 mL of water following consumption of 4 oz of applesauce. | |

Primary: Maximum Observed Plasma Concentration (C_{max}) of Cinacalcet

| | |
|--|---|
| End point title | Maximum Observed Plasma Concentration (C _{max}) of Cinacalcet |
| End point description: Cinacalcet in plasma samples was assessed using high performance liquid chromatography followed by tandem mass spectrometric detection (LC-MS/MS). Cinacalcet concentrations below the lower limit of quantitation (LLOQ, 0.100 ng/mL) were set to zero before data analysis. | |
| End point type | Primary |
| End point timeframe: Predose and up to 72 hours post-dose | |

| End point values | Cinacalcet 30 mg Capsule | Cinacalcet 30 mg Tablet | | |
|--------------------------------------|--------------------------|-------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 44 | 43 | | |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | 6.07 (± 3.62) | 5.97 (± 3.38) | | |

Statistical analyses

| | |
|--|--|
| Statistical analysis title | Statistical Evaluation of C _{max} |
| Statistical analysis description: C _{max} was natural log-transformed and analyzed using a mixed-effect analysis of variance (ANOVA) model. The effects due to sequence, period, and formulation were evaluated as fixed effects, and subject within sequence was treated as a random effect. The mean difference and 90% CI between the 2 treatment formulations was calculated and then transformed back to report the ratio of the geometric means and the 90% CI of the ratio. The number of subjects included in the analysis is 43, not 87. | |
| Comparison groups | Cinacalcet 30 mg Capsule v Cinacalcet 30 mg Tablet |

| | |
|---|----------------------------|
| Number of subjects included in analysis | 87 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence ^[1] |
| Parameter estimate | Ratio of Capsule:Tablet |
| Point estimate | 0.998 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 0.885 |
| upper limit | 1.126 |

Notes:

[1] - The two formulations administered in treatments A and B were considered bioequivalent if the 90% confidence intervals for the ratio of the C_{max}, AUC_{0-t}, and AUC_{0-inf} geometric means were between 0.80 to 1.25.

Primary: Area Under the Plasma Drug Concentration-Time Curve From Time Zero to The Time of the Last Quantifiable Concentration (AUClast)

| | |
|-----------------|---|
| End point title | Area Under the Plasma Drug Concentration-Time Curve From Time Zero to The Time of the Last Quantifiable Concentration (AUClast) |
|-----------------|---|

End point description:

The area under the plasma drug concentration-time curve from time zero to the time of the last quantifiable concentration (AUClast), estimated using the linear trapezoidal method (for assessment of the AUC_{0-t} endpoint).

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Predose to 72 hours post-dose

| End point values | Cinacalcet 30 mg Capsule | Cinacalcet 30 mg Tablet | | |
|--------------------------------------|--------------------------|-------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 44 | 43 | | |
| Units: hr*ng/mL | | | | |
| arithmetic mean (standard deviation) | 57.0 (± 34.0) | 60.4 (± 39.1) | | |

Statistical analyses

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical Evaluation of AUClast |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

AUClast was natural log-transformed and analyzed using a mixed-effect ANOVA model. The effects due to sequence, period, and formulation were evaluated as fixed effects, and subject within sequence was treated as a random effect. The mean difference and the corresponding 90% CI between the 2 treatment formulations was calculated and then transformed back to report the ratio of the geometric means and the 90% CI of the ratio.

The number of subjects included in the analysis is 43, not 87.

| | |
|-------------------|--|
| Comparison groups | Cinacalcet 30 mg Capsule v Cinacalcet 30 mg Tablet |
|-------------------|--|

| | |
|---|----------------------------|
| Number of subjects included in analysis | 87 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence ^[2] |
| Parameter estimate | Ratio of Capsule:Tablet |
| Point estimate | 0.945 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 0.861 |
| upper limit | 1.039 |

Notes:

[2] - The two formulations administered in treatments A and B were considered bioequivalent if the 90% confidence intervals for the ratio of the C_{max}, AUC_{0-t}, and AUC_{0-inf} geometric means were between 0.80 to 1.25.

Primary: Area Under the Plasma Drug Concentration-Time Curve From Time Zero to Infinity (AUC_{inf})

| | |
|--------------------------------------|--|
| End point title | Area Under the Plasma Drug Concentration-Time Curve From Time Zero to Infinity (AUC _{inf}) |
| End point description: | |
| End point type | Primary |
| End point timeframe: | |
| Predose and up to 72 hours post-dose | |

| End point values | Cinacalcet 30 mg Capsule | Cinacalcet 30 mg Tablet | | |
|--------------------------------------|--------------------------|-------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 42 | 43 | | |
| Units: hr*ng/mL | | | | |
| arithmetic mean (standard deviation) | 63.5 (± 36.4) | 66.1 (± 43.2) | | |

Statistical analyses

| | |
|--|--|
| Statistical analysis title | Statistical Evaluation of AUC _{inf} |
| Statistical analysis description: | |
| AUC _{inf} was natural log-transformed and analyzed using a mixed-effect ANOVA model. The effects due to sequence, period, and formulation were evaluated as fixed effects, and subject within sequence was treated as a random effect. The mean difference and the corresponding 90% CI between the 2 treatment formulations was calculated and then transformed back to report the ratio of the geometric means and the 90% CI of the ratio. | |
| The number of subjects included in the analysis is 43, not 85. | |
| Comparison groups | Cinacalcet 30 mg Capsule v Cinacalcet 30 mg Tablet |
| Number of subjects included in analysis | 85 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence ^[3] |
| Parameter estimate | Ratio of Capsule:Tablet |
| Point estimate | 0.947 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 0.861 |
| upper limit | 1.042 |

Notes:

[3] - The two formulations administered in treatments A and B were considered bioequivalent if the 90% confidence intervals for the ratio of the C_{max}, AUC_{0-t}, and AUC_{0-inf} geometric means were between 0.80 to 1.25.

Secondary: Number of Participants with Adverse Events

| | |
|-----------------|--|
| End point title | Number of Participants with Adverse Events |
|-----------------|--|

End point description:

The severity of each adverse event was graded using Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 criteria.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From first dose of the investigational product in period 1 to day 14 (7 days in each treatment period).

| End point values | Cinacalcet 30 mg Capsule | Cinacalcet 30 mg Tablet | | |
|---|--------------------------|-------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 44 | 43 | | |
| Units: participants | | | | |
| Any adverse event (AE) | 8 | 4 | | |
| AE Grade ≥ 2 | 1 | 0 | | |
| AE Grade ≥ 3 | 0 | 0 | | |
| AE Grade ≥ 4 | 0 | 0 | | |
| Serious adverse events (SAE) | 0 | 0 | | |
| AE leading to discontinuation of cinacalcet | 0 | 0 | | |
| Fatal adverse events | 0 | 0 | | |
| Treatment-related adverse event | 3 | 2 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Maximum Observed Concentration of Cinacalcet

| | |
|-----------------|--|
| End point title | Time to Maximum Observed Concentration of Cinacalcet |
|-----------------|--|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Predose to 72 hours post-dose

| End point values | Cinacalcet 30 mg Capsule | Cinacalcet 30 mg Tablet | | |
|-------------------------------|--------------------------|-------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 44 | 43 | | |
| Units: hours | | | | |
| median (full range (min-max)) | 2.5 (1.0 to 6.0) | 3.5 (1.0 to 8.0) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Half-life of Cinacalcet (T_{1/2})

| | |
|-------------------------------|---|
| End point title | Half-life of Cinacalcet (T _{1/2}) |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Predose to 72 hours post-dose | |

| End point values | Cinacalcet 30 mg Capsule | Cinacalcet 30 mg Tablet | | |
|--------------------------------------|--------------------------|-------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 42 | 43 | | |
| Units: hours | | | | |
| arithmetic mean (standard deviation) | 21.6 (± 9.58) | 20.6 (± 9.19) | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

14 Days (7 days in each treatment period)

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 19.1 |
|--------------------|------|

Reporting groups

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|-----------------------|--------------------------|
| Reporting group title | Cinacalcet 30 mg Capsule |
|-----------------------|--------------------------|

Reporting group description:

Participants received a single 30-mg oral dose of cinacalcet given as the contents of six 5-mg capsules sprinkled over 4 oz of applesauce and consumed within 1 minute with 240 mL of water.

| | |
|-----------------------|-------------------------|
| Reporting group title | Cinacalcet 30 mg Tablet |
|-----------------------|-------------------------|

Reporting group description:

Participants received a single 30-mg oral dose of cinacalcet given as one 30-mg tablet swallowed whole with 240 mL of water following consumption of 4 oz of applesauce.

| | |
|-----------------------|--------------|
| Reporting group title | All Subjects |
|-----------------------|--------------|

Reporting group description:

Participants received Treatment A (contents of six 5-mg capsules of cinacalcet sprinkled over 4 oz of applesauce), and Treatment B (a single 30-mg tablet of cinacalcet with 4 oz of applesauce) in 1 of 2 sequences: AB or BA, separated by a washout period of at least 7 days.

| Serious adverse events | Cinacalcet 30 mg Capsule | Cinacalcet 30 mg Tablet | All Subjects |
|---|--------------------------|-------------------------|----------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 43 (0.00%) | 0 / 44 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | | | |

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

| Non-serious adverse events | Cinacalcet 30 mg Capsule | Cinacalcet 30 mg Tablet | All Subjects |
|---|--------------------------|-------------------------|------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 8 / 44 (18.18%) | 4 / 43 (9.30%) | 11 / 44 (25.00%) |
| Injury, poisoning and procedural complications | | | |
| Arthropod bite | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 43 (0.00%) | 1 / 44 (2.27%) |
| occurrences (all) | 1 | 0 | 1 |
| Laceration | | | |

| | | | |
|---|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 1 / 43 (2.33%) 1 | 1 / 44 (2.27%) 1 |
| Skin abrasion subjects affected / exposed occurrences (all) | 1 / 44 (2.27%) 1 | 0 / 43 (0.00%) 0 | 1 / 44 (2.27%) 1 |
| Skin injury subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 1 / 43 (2.33%) 1 | 1 / 44 (2.27%) 1 |
| Nervous system disorders Dizziness subjects affected / exposed occurrences (all) | 1 / 44 (2.27%) 1 | 0 / 43 (0.00%) 0 | 1 / 44 (2.27%) 1 |
| Headache subjects affected / exposed occurrences (all) | 3 / 44 (6.82%) 3 | 0 / 43 (0.00%) 0 | 3 / 44 (6.82%) 3 |
| Somnolence subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 1 / 43 (2.33%) 1 | 1 / 44 (2.27%) 1 |
| General disorders and administration site conditions Chills subjects affected / exposed occurrences (all) | 1 / 44 (2.27%) 1 | 0 / 43 (0.00%) 0 | 1 / 44 (2.27%) 1 |
| Fatigue subjects affected / exposed occurrences (all) | 1 / 44 (2.27%) 1 | 0 / 43 (0.00%) 0 | 1 / 44 (2.27%) 1 |
| Ear and labyrinth disorders Ear discomfort subjects affected / exposed occurrences (all) | 1 / 44 (2.27%) 1 | 0 / 43 (0.00%) 0 | 1 / 44 (2.27%) 1 |
| Gastrointestinal disorders Abdominal discomfort subjects affected / exposed occurrences (all) | 2 / 44 (4.55%) 2 | 0 / 43 (0.00%) 0 | 2 / 44 (4.55%) 2 |
| Diarrhoea subjects affected / exposed occurrences (all) | 2 / 44 (4.55%) 2 | 1 / 43 (2.33%) 1 | 2 / 44 (4.55%) 3 |

| | | | |
|--|---------------------|---------------------|---------------------|
| Gastrooesophageal reflux disease subjects affected / exposed occurrences (all) | 1 / 44 (2.27%) 1 | 1 / 43 (2.33%) 1 | 2 / 44 (4.55%) 2 |
| Nausea subjects affected / exposed occurrences (all) | 1 / 44 (2.27%) 1 | 1 / 43 (2.33%) 1 | 2 / 44 (4.55%) 2 |
| Vomiting subjects affected / exposed occurrences (all) | 1 / 44 (2.27%) 1 | 0 / 43 (0.00%) 0 | 1 / 44 (2.27%) 1 |
| Musculoskeletal and connective tissue disorders Pain in extremity subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 1 / 43 (2.33%) 1 | 1 / 44 (2.27%) 1 |
| Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) | 1 / 44 (2.27%) 1 | 0 / 43 (0.00%) 0 | 1 / 44 (2.27%) 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