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Trial record **1 of 1** for: CSPP100A2252

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# Effects of Aliskiren, Ramipril, and the Combination on Levels of Angiotensin II in Patients With Decompensated Systolic Heart Failure (ESCAPE-SHF)

**This study has been completed.**

**Sponsor:**
Novartis Pharmaceuticals

**Information provided by (Responsible Party):**
Novartis ( Novartis Pharmaceuticals )

**ClinicalTrials.gov Identifier:**
NCT00923156

First received: June 17, 2009
Last updated: July 19, 2012
Last verified: July 2012
History of Changes

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Results First Received: February 1, 2012

| | |
|---|---|
| **Study Type:** | Interventional |
| **Study Design:** | Allocation: Randomized; Intervention Model: Parallel Assignment;<br>Masking: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor);<br>Primary Purpose: Treatment |
| **Condition:** | Heart Failure |
| **Interventions:** | Drug: aliskiren<br>Drug: ramipril<br>Drug: Placebo to aliskiren<br>Drug: Placebo to ramipril |

## Participant Flow

Hide Participant Flow

### Recruitment Details

| Key information relevant to the recruitment process for the overall study, such as dates of the recruitment period and locations |
|---|
| No text entered. |

### Pre-Assignment Details

| Significant events and approaches for the overall study following participant enrollment, but prior to group assignment |
|---|
| Patient enrolled to 4 week open label run-in phase (period 1) to up-titrate ramipril dose. 123 patients were randomized on Day 1 of Period 2 in a double-blind fashion to one of the three (1:1:1) treatment arms. The double-blind period was for 12 weeks. |

### Reporting Groups

| | Description |
|---|---|
| **Aliskiren** | In open label run-in phase (period 1), patients started with ramipril 2.5 mg or 5.0 mg capsule once daily (o.d) depending on previous treatment with RAAS blockers and up-titrated to ramipril 10 mg capsule o.d by end of period 1. In double blind phase (Period 2), patients received aliskiren (150 mg once daily) up titrated to 300 mg once daily after 1 week of treatment following a clinical safety patient assessment at the study site and matching placebo of ramipril capsules. |
| **Ramipril** | In open label run-in phase (period 1), patients started with ramipril 2.5 mg or 5.0 mg capsule once daily (o.d) |

| | |
|---|---|
| | depending on previous treatment with RAAS blockers and up-titrated to ramipril 10 mg capsule o.d by end of period 1.<br>In double blind phase (Period 2), patients received ramipril 10 mg capsule o.d and matching placebo of aliskiren tablet. |
| **Aliskiren Plus Ramipril** | In open label run-in phase (period 1), patients started with ramipril 2.5 mg or 5.0 mg capsule once daily (o.d) depending on previous treatment with RAAS blockers and up-titrated to ramipril 10 mg capsule o.d by end of period 1.<br>In double blind phase (period 2), patients received ramipril (10 mg once daily capsule) and aliskiren (150 mg once daily tablet) up titrated to 300 mg once daily after 1 week of treatment following a clinical safety patient assessment at the study site. |

**Participant Flow: Overall Study**

| | Aliskiren | Ramipril | Aliskiren Plus Ramipril |
|---|---|---|---|
| **STARTED** | 40 [1] | 42 | 41 |
| **COMPLETED** | 40 | 38 | 38 |
| **NOT COMPLETED** | 0 | 4 | 3 |
| **Adverse Event** | 0 | 2 | 1 |
| **Abnormal laboratory values** | 0 | 0 | 1 |
| **Withdrawal by Subject** | 0 | 1 | 0 |
| **Death** | 0 | 1 | 0 |
| **Lack of Efficacy** | 0 | 0 | 1 |

[1] "Started" indicates randomized, safety and pharmacodynamic population

## Baseline Characteristics

Hide Baseline Characteristics

**Population Description**

| **Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.** |
|---|
| No text entered. |

**Reporting Groups**

| | Description |
|---|---|
| **Aliskiren** | In open label run-in phase (period 1), patients started with ramipril 2.5 mg or 5.0 mg capsule once daily (o.d) depending on previous treatment with RAAS blockers and up-titrated to ramipril 10 mg capsule o.d by end of period 1. In double blind phase (Period 2), patients received aliskiren (150 mg once daily) up titrated to 300 mg once daily after 1 week of treatment following a clinical safety patient assessment at the study site and matching placebo of ramipril capsules. |
| **Ramipril** | In open label run-in phase (period 1), patients started with ramipril 2.5 mg or 5.0 mg capsule once daily (o.d) depending on previous treatment with RAAS blockers and up-titrated to ramipril 10 mg capsule o.d by end of period 1.<br>In double blind phase (Period 2), patients received ramipril 10 mg capsule o.d and matching placebo of aliskiren tablet. |
| **Aliskiren Plus Ramipril** | In open label run-in phase (period 1), patients started with ramipril 2.5 mg or 5.0 mg capsule once daily (o.d) depending on previous treatment with RAAS blockers and up-titrated to ramipril 10 mg capsule o.d by end of period 1.<br>In double blind phase (period 2), patients received ramipril (10 mg once daily capsule) and aliskiren (150 mg once daily tablet) up titrated to 300 mg once daily after 1 week of treatment following a clinical safety patient assessment at the study site. |

| | |
|---|---|
| **Total** | Total of all reporting groups |

**Baseline Measures**

| | Aliskiren | Ramipril | Aliskiren Plus Ramipril | Total |
|---|---|---|---|---|
| **Number of Participants [units: participants]** | **40** | **42** | **41** | **123** |
| **Age [units: years] Mean (Standard Deviation)** | **61.3 (9.00)** | **64.3 (9.91)** | **62.0 (10.47)** | **62.6 (9.83)** |
| **Gender [units: participants]** | | | | |
| **Female** | **11** | **8** | **7** | **26** |
| **Male** | **29** | **34** | **34** | **97** |

## Outcome Measures

Hide All Outcome Measures

1. Primary: Venous Angiotensin II Levels After 12 Weeks of Treatment [ Time Frame: Baseline. 12 Weeks (Day 84, period 2) ]

| | |
|---|---|
| **Measure Type** | Primary |
| **Measure Title** | Venous Angiotensin II Levels After 12 Weeks of Treatment |
| **Measure Description** | Peripheral venous blood was collected after 30 minutes of rest in the sitting position for analysis of biomarkers. Geometric mean ratio to baseline at Week 12 for Venous angiotensin II levels was calculated in patients with decompensated systolic heart failure (SHF) and left ventricular ejection fraction ≤40% at 0 hour pre-dose, 3 hours and 24 hours post-dose. |
| **Time Frame** | Baseline. 12 Weeks (Day 84, period 2) |
| **Safety Issue** | No |

**Population Description**

| |
|---|
| **Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.** |
| Pharmacodynamic (PD) Analysis Set: Subjects with any available PD data and no major protocol deviations with impact on PD data. Only patients with a value at both baseline and post-dose are included. In each category "n" indicates patients with observations at that time point. |

**Reporting Groups**

| | Description |
|---|---|
| **Aliskiren** | In open label run-in phase (period 1), patients started with ramipril 2.5 mg or 5.0 mg capsule once daily (o.d) depending on previous treatment with RAAS blockers and up-titrated to ramipril 10 mg capsule o.d by end of period 1. In double blind phase (Period 2), patients received aliskiren (150 mg once daily) up titrated to 300 mg once daily after 1 week of treatment following a clinical safety patient assessment at the study site and matching placebo of ramipril capsules. |
| **Ramipril** | In open label run-in phase (period 1), patients started with ramipril 2.5 mg or 5.0 mg capsule once daily (o.d) depending on previous treatment with RAAS blockers and up-titrated to ramipril 10 mg capsule o.d by end of period 1.<br>In double blind phase (Period 2), patients received ramipril 10 mg capsule o.d and matching placebo of aliskiren tablet. |
| **Aliskiren Plus Ramipril** | In open label run-in phase (period 1), patients started with ramipril 2.5 mg or 5.0 mg capsule once daily (o.d) depending on previous treatment with RAAS blockers and up-titrated to ramipril 10 mg capsule o.d by end of period 1.<br>In double blind phase (period 2), patients received ramipril (10 mg once daily capsule) and aliskiren (150 mg once |

| | |
|---|---|
| | daily tablet) up titrated to 300 mg once daily after 1 week of treatment following a clinical safety patient assessment at the study site. |

**Measured Values**

| | Aliskiren | Ramipril | Aliskiren Plus Ramipril |
|---|---|---|---|
| **Number of Participants Analyzed [units: participants]** | **40** | **42** | **41** |
| **Venous Angiotensin II Levels After 12 Weeks of Treatment [units: ratio] Geometric Mean (95% Confidence Interval)** | | | |
| **0 Hour pre-dose (n=40, 38, 37)** | **0.91 (0.52 to 1.59)** | **1.08 (0.64 to 1.81)** | **0.66 (0.37 to 1.18)** |
| **3 hour post-dose (n=40, 38, 38)** | **0.38 (0.23 to 0.62)** | **0.44 (0.24 to 0.78)** | **0.38 (0.22 to 0.66)** |
| **24 hour post-dose (n=40, 38, 38)** | **0.79 (0.44 to 1.41)** | **0.97 (0.59 to 1.60)** | **0.64 (0.34 to 1.24)** |

**No statistical analysis provided for Venous Angiotensin II Levels After 12 Weeks of Treatment**

2. Secondary: Biomarker Plasma Renin Concentration (PRC)After 12 Weeks of Treatment [ Time Frame: Baseline, 12 weeks (84 days, period 2) ]

| | |
|---|---|
| **Measure Type** | Secondary |
| **Measure Title** | Biomarker Plasma Renin Concentration (PRC)After 12 Weeks of Treatment |
| **Measure Description** | Peripheral venous blood was collected after 30 minutes of rest in the sitting position for analysis of biomarkers. Geometric Mean Ratio to baseline at 12 weeks for PRC was calculated at 0 hour pre-dose. |
| **Time Frame** | Baseline, 12 weeks (84 days, period 2) |
| **Safety Issue** | No |

**Population Description**

| |
|---|
| **Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.** |
| Pharmacodynamic (PD) Analysis Set: Subjects with any available PD data and no major protocol deviations with impact on PD data. Only patients with a value at both baseline and post-dose are included. |

**Reporting Groups**

| | Description |
|---|---|
| **Aliskiren** | In open label run-in phase (period 1), patients started with ramipril 2.5 mg or 5.0 mg capsule once daily (o.d) depending on previous treatment with RAAS blockers and up-titrated to ramipril 10 mg capsule o.d by end of period 1. In double blind phase (Period 2), patients received aliskiren (150 mg once daily) up titrated to 300 mg once daily after 1 week of treatment following a clinical safety patient assessment at the study site and matching placebo of ramipril capsules. |
| **Ramipril** | In open label run-in phase (period 1), patients started with ramipril 2.5 mg or 5.0 mg capsule once daily (o.d) depending on previous treatment with RAAS blockers and up-titrated to ramipril 10 mg capsule o.d by end of period 1.<br>In double blind phase (Period 2), patients received ramipril 10 mg capsule o.d and matching placebo of aliskiren tablet. |
| **Aliskiren Plus Ramipril** | In open label run-in phase (period 1), patients started with ramipril 2.5 mg or 5.0 mg capsule once daily (o.d) depending on previous treatment with RAAS blockers and up-titrated to ramipril 10 mg capsule o.d by end of period 1. |

| | |
|---|---|
| | In double blind phase (period 2), patients received ramipril (10 mg once daily capsule) and aliskiren (150 mg once daily tablet) up titrated to 300 mg once daily after 1 week of treatment following a clinical safety patient assessment at the study site. |

**Measured Values**

| | Aliskiren | Ramipril | Aliskiren Plus Ramipril |
|---|---|---|---|
| **Number of Participants Analyzed [units: participants]** | **40** | **38** | **37** |
| **Biomarker Plasma Renin Concentration (PRC)After 12 Weeks of Treatment [units: ratio] Geometric Mean (95% Confidence Interval)** | **2.48 (1.67 to 3.66)** | **0.96 (0.71 to 1.30)** | **4.67 (2.80 to 7.78)** |

**No statistical analysis provided for Biomarker Plasma Renin Concentration (PRC)After 12 Weeks of Treatment**

3. Secondary: Biomarker Trapping Plasma Renin Activity (tPRA) After 12 Weeks of Treatment [ Time Frame: Baseline,12 weeks (84 days, Period 2) ]

| | |
|---|---|
| **Measure Type** | Secondary |
| **Measure Title** | Biomarker Trapping Plasma Renin Activity (tPRA) After 12 Weeks of Treatment |
| **Measure Description** | Peripheral venous blood was collected after 30 minutes of rest in the sitting position for analysis of biomarkers. Geometric Mean Ratio to baseline at Week 12 for tPRA was calculated at 0 hour pre-dose, 3 hour and 24 hour post-dose. |
| **Time Frame** | Baseline,12 weeks (84 days, Period 2) |
| **Safety Issue** | No |

**Population Description**

| |
|---|
| **Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.** |
| Pharmacodynamic (PD) Analysis Set: Subjects with any available PD data and no major protocol deviations with impact on PD data. Only patients with a value at both baseline and post-dose are included. In each category "n" indicates patients with observations at that time point. |

**Reporting Groups**

| | Description |
|---|---|
| **Aliskiren** | In open label run-in phase (period 1), patients started with ramipril 2.5 mg or 5.0 mg capsule once daily (o.d) depending on previous treatment with RAAS blockers and up-titrated to ramipril 10 mg capsule o.d by end of period 1. In double blind phase (Period 2), patients received aliskiren (150 mg once daily) up titrated to 300 mg once daily after 1 week of treatment following a clinical safety patient assessment at the study site and matching placebo of ramipril capsules. |
| **Ramipril** | In open label run-in phase (period 1), patients started with ramipril 2.5 mg or 5.0 mg capsule once daily (o.d) depending on previous treatment with RAAS blockers and up-titrated to ramipril 10 mg capsule o.d by end of period 1.<br>In double blind phase (Period 2), patients received ramipril 10 mg capsule o.d and matching placebo of aliskiren tablet. |
| **Aliskiren Plus Ramipril** | In open label run-in phase (period 1), patients started with ramipril 2.5 mg or 5.0 mg capsule once daily (o.d) depending on previous treatment with RAAS blockers and up-titrated to ramipril 10 mg capsule o.d by end of period 1.<br>In double blind phase (period 2), patients received ramipril (10 mg once daily capsule) and aliskiren (150 mg once daily tablet) up titrated to 300 mg once daily after 1 week of treatment following a clinical safety patient assessment at the study site. |

**Measured Values**

| | Aliskiren | Ramipril | Aliskiren Plus Ramipril |
|---|---|---|---|
| **Number of Participants Analyzed [units: participants]** | **40** | **42** | **41** |
| **Biomarker Trapping Plasma Renin Activity (tPRA) After 12 Weeks of Treatment [units: ratio] Geometric Mean (95% Confidence Interval)** | | | |
| **0 hour pre-dose (n=40,38,37)** | **0.14 (0.08 to 0.24)** | **1.02 (0.68 to 1.52)** | **0.25 (0.15 to 0.41)** |
| **3 hour post-dose (n=40,38,38)** | **0.07 (0.04 to 0.14)** | **1.50 (0.86 to 2.61)** | **0.15 (0.09 to 0.24)** |
| **24 hour post-dose (n=40,38,38)** | **0.12 (0.07 to 0.22)** | **0.90 (0.58 to 1.40)** | **0.16 (0.11 to 0.25)** |

**No statistical analysis provided for Biomarker Trapping Plasma Renin Activity (tPRA) After 12 Weeks of Treatment**

4. Secondary: Biomarker B-type Natriuretic Peptide (BNP) After 12 Weeks of Treatment [ Time Frame: Baseline, 12 weeks (Day 84 period 2) ]

| | |
|---|---|
| **Measure Type** | Secondary |
| **Measure Title** | Biomarker B-type Natriuretic Peptide (BNP) After 12 Weeks of Treatment |
| **Measure Description** | Peripheral venous blood was collected after 30 minutes of rest in the sitting position for analysis of biomarkers. Geometric Mean Ratio to baseline at Week 12 for BNP was calculated at 0 hours pre-dose. |
| **Time Frame** | Baseline, 12 weeks (Day 84 period 2) |
| **Safety Issue** | No |

**Population Description**

| **Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.** |
|---|
| Pharmacodynamic (PD) Analysis Set: Subjects with any available PD data and no major protocol deviations with impact on PD data. Only patients with a value at both baseline and post-dose are included. |

**Reporting Groups**

| | Description |
|---|---|
| **Aliskiren** | In open label run-in phase (period 1), patients started with ramipril 2.5 mg or 5.0 mg capsule once daily (o.d) depending on previous treatment with RAAS blockers and up-titrated to ramipril 10 mg capsule o.d by end of period 1. In double blind phase (Period 2), patients received aliskiren (150 mg once daily) up titrated to 300 mg once daily after 1 week of treatment following a clinical safety patient assessment at the study site and matching placebo of ramipril capsules. |
| **Ramipril** | In open label run-in phase (period 1), patients started with ramipril 2.5 mg or 5.0 mg capsule once daily (o.d) depending on previous treatment with RAAS blockers and up-titrated to ramipril 10 mg capsule o.d by end of period 1.<br>In double blind phase (Period 2), patients received ramipril 10 mg capsule o.d and matching placebo of aliskiren tablet. |
| **Aliskiren Plus Ramipril** | In open label run-in phase (period 1), patients started with ramipril 2.5 mg or 5.0 mg capsule once daily (o.d) depending on previous treatment with RAAS blockers and up-titrated to ramipril 10 mg capsule o.d by end of period 1.<br>In double blind phase (period 2), patients received ramipril (10 mg once daily capsule) and aliskiren (150 mg once |

| | |
|---|---|
| | daily tablet) up titrated to 300 mg once daily after 1 week of treatment following a clinical safety patient assessment at the study site. |

**Measured Values**

| | Aliskiren | Ramipril | Aliskiren Plus Ramipril |
|---|---|---|---|
| **Number of Participants Analyzed [units: participants]** | **40** | **38** | **37** |
| **Biomarker B-type Natriuretic Peptide (BNP) After 12 Weeks of Treatment [units: ratio] Geometric Mean (95% Confidence Interval)** | **0.96 (0.80 to 1.16)** | **0.84 (0.69 to 1.03)** | **0.78 (0.64 to 0.95)** |

**No statistical analysis provided for Biomarker B-type Natriuretic Peptide (BNP) After 12 Weeks of Treatment**

5. Secondary: Biomarker Urinary Aldosterone After 12 Weeks of Treatment [ Time Frame: Baseline,12 weeks (Day 84 period 2) ]

| | |
|---|---|
| **Measure Type** | Secondary |
| **Measure Title** | Biomarker Urinary Aldosterone After 12 Weeks of Treatment |
| **Measure Description** | 24 hour urine collections were performed. Geometric Mean Ratio to baseline at Week 12 for Urinary aldosterone was calculated 24 hours post-dose. |
| **Time Frame** | Baseline,12 weeks (Day 84 period 2) |
| **Safety Issue** | No |

**Population Description**

| |
|---|
| **Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.** |
| Pharmacodynamic (PD) Analysis Set: Subjects with any available PD data and no major protocol deviations with impact on PD data. Only patients with a value at both baseline and post-dose are included. |

**Reporting Groups**

| | Description |
|---|---|
| **Aliskiren** | In open label run-in phase (period 1), patients started with ramipril 2.5 mg or 5.0 mg capsule once daily (o.d) depending on previous treatment with RAAS blockers and up-titrated to ramipril 10 mg capsule o.d by end of period 1. In double blind phase (Period 2), patients received aliskiren (150 mg once daily) up titrated to 300 mg once daily after 1 week of treatment following a clinical safety patient assessment at the study site and matching placebo of ramipril capsules. |
| **Ramipril** | In open label run-in phase (period 1), patients started with ramipril 2.5 mg or 5.0 mg capsule once daily (o.d) depending on previous treatment with RAAS blockers and up-titrated to ramipril 10 mg capsule o.d by end of period 1.<br>In double blind phase (Period 2), patients received ramipril 10 mg capsule o.d and matching placebo of aliskiren tablet. |
| **Aliskiren Plus Ramipril** | In open label run-in phase (period 1), patients started with ramipril 2.5 mg or 5.0 mg capsule once daily (o.d) depending on previous treatment with RAAS blockers and up-titrated to ramipril 10 mg capsule o.d by end of period 1.<br>In double blind phase (period 2), patients received ramipril (10 mg once daily capsule) and aliskiren (150 mg once daily tablet) up titrated to 300 mg once daily after 1 week of treatment following a clinical safety patient assessment at the study site. |

**Measured Values**

| | Aliskiren | Ramipril | Aliskiren Plus Ramipril |
|---|---|---|---|

| | | | |
|---|---|---|---|
| **Number of Participants Analyzed [units: participants]** | **40** | **37** | **36** |
| **Biomarker Urinary Aldosterone After 12 Weeks of Treatment [units: ratio] Geometric Mean (95% Confidence Interval)** | **0.83 (0.64 to 1.08)** | **0.96 (0.78 to 1.18)** | **0.87 (0.63 to 1.21)** |

**No statistical analysis provided for Biomarker Urinary Aldosterone After 12 Weeks of Treatment**

6. Secondary: Pharmacokinetic of Aliskiren: Time to Reach the Maximum Concentration (Tmax) After Drug Administration [ Time Frame: 12 weeks ]

| | |
|---|---|
| **Measure Type** | Secondary |
| **Measure Title** | Pharmacokinetic of Aliskiren: Time to Reach the Maximum Concentration (Tmax) After Drug Administration |
| **Measure Description** | Blood samples (2 mL) for the determination of aliskiren concentration in plasma were collected using an indwelling cannula inserted in a forearm vein. Samples were collected at week 12 (day 84): pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10 and 24 hours post-dose. |
| **Time Frame** | 12 weeks |
| **Safety Issue** | No |

**Population Description**

| |
|---|
| **Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.** |
| All subjects with evaluable PK parameter data and no major protocol deviations with impact on PK data were included in the PK data analysis. |

**Reporting Groups**

| | **Description** |
|---|---|
| **Aliskiren** | In open label run-in phase (period 1), patients started with ramipril 2.5 mg or 5.0 mg capsule once daily (o.d) depending on previous treatment with RAAS blockers and up-titrated to ramipril 10 mg capsule o.d by end of period 1. In double blind phase (Period 2), patients received aliskiren (150 mg once daily) up titrated to 300 mg once daily after 1 week of treatment following a clinical safety patient assessment at the study site and matching placebo of ramipril capsules. |

**Measured Values**

| | **Aliskiren** |
|---|---|
| **Number of Participants Analyzed [units: participants]** | **40** |
| **Pharmacokinetic of Aliskiren: Time to Reach the Maximum Concentration (Tmax) After Drug Administration [units: Hour] Median (Full Range)** | **1.50 (0.42 to 7.97)** |

**No statistical analysis provided for Pharmacokinetic of Aliskiren: Time to Reach the Maximum Concentration (Tmax) After Drug Administration**

7. Secondary: Pharmacokinetic of Aliskiren: The Observed Maximum Plasma Concentration (Cmax) Following Drug Administration [ Time Frame: 12 weeks ]

| | |
|---|---|
| **Measure Type** | Secondary |
| **Measure Title** | Pharmacokinetic of Aliskiren: The Observed Maximum Plasma Concentration (Cmax) Following Drug Administration |
| **Measure Description** | Blood samples (2 mL) for the determination of aliskiren concentration in plasma were collected using an indwelling cannula inserted in a forearm vein. Samples were collected at week 12 (day 84): pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10 and 24 hours post-dose. |

| | |
|---|---|
| **Time Frame** | 12 weeks |
| **Safety Issue** | No |

**Population Description**

| **Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.** |
|---|
| All subjects with evaluable PK parameter data and no major protocol deviations with impact on PK data were included in the PK data analysis. |

**Reporting Groups**

| | **Description** |
|---|---|
| **Aliskiren** | In open label run-in phase (period 1), patients started with ramipril 2.5 mg or 5.0 mg capsule once daily (o.d) depending on previous treatment with RAAS blockers and up-titrated to ramipril 10 mg capsule o.d by end of period 1. In double blind phase (Period 2), patients received aliskiren (150 mg once daily) up titrated to 300 mg once daily after 1 week of treatment following a clinical safety patient assessment at the study site and matching placebo of ramipril capsules. |

**Measured Values**

| | **Aliskiren** |
|---|---|
| **Number of Participants Analyzed [units: participants]** | **40** |
| **Pharmacokinetic of Aliskiren: The Observed Maximum Plasma Concentration (Cmax) Following Drug Administration [units: ng/mL] Mean (Standard Deviation)** | **257.2 (270.23)** |

**No statistical analysis provided for Pharmacokinetic of Aliskiren: The Observed Maximum Plasma Concentration (Cmax) Following Drug Administration**

8. Secondary: Pharmacokinetic of Aliskiren: The Area Under the Plasma Concentration-time Curve From Time Zero to the End of the Dosing Interval Tau(AUCtau) [ Time Frame: 12 weeks ]

| | |
|---|---|
| **Measure Type** | Secondary |
| **Measure Title** | Pharmacokinetic of Aliskiren: The Area Under the Plasma Concentration-time Curve From Time Zero to the End of the Dosing Interval Tau(AUCtau) |
| **Measure Description** | Blood samples (2 mL) for the determination of aliskiren concentration in plasma were collected using an indwelling cannula inserted in a forearm vein. Samples were collected at week 12 (day 84): pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10 and 24 hours post-dose. |
| **Time Frame** | 12 weeks |
| **Safety Issue** | No |

**Population Description**

| **Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.** |
|---|
| All subjects with evaluable PK parameter data and no major protocol deviations with impact on PK data were included in the PK data analysis. |

**Reporting Groups**

| | **Description** |
|---|---|
| **Aliskiren** | In open label run-in phase (period 1), patients started with ramipril 2.5 mg or 5.0 mg capsule once daily (o.d) depending on previous treatment with RAAS blockers and up-titrated to ramipril 10 mg capsule o.d by end of period 1. In double blind phase (Period 2), patients received aliskiren (150 mg once daily) up titrated to 300 mg once daily after 1 week of treatment following a clinical safety patient assessment at the study site and matching placebo of ramipril capsules. |

**Measured Values**

| | Aliskiren |
|---|---|
| **Number of Participants Analyzed [units: participants]** | **40** |
| **Pharmacokinetic of Aliskiren: The Area Under the Plasma Concentration-time Curve From Time Zero to the End of the Dosing Interval Tau(AUCtau) [units: hr*ng/mL] Mean (Standard Deviation)** | **1707 (1321.9)** |

**No statistical analysis provided for Pharmacokinetic of Aliskiren: The Area Under the Plasma Concentration-time Curve From Time Zero to the End of the Dosing Interval Tau(AUCtau)**

9. Secondary: Pharmacokinetic of Aliskiren: The Area Under the Plasma Concentration-time Curve From Time Zero to the Time of the Last Quantifiable Concentration (AUClast) [ Time Frame: 12 weeks ]

| | |
|---|---|
| **Measure Type** | Secondary |
| **Measure Title** | Pharmacokinetic of Aliskiren: The Area Under the Plasma Concentration-time Curve From Time Zero to the Time of the Last Quantifiable Concentration (AUClast) |
| **Measure Description** | Blood samples (2 mL) for the determination of aliskiren concentration in plasma were collected using an indwelling cannula inserted in a forearm vein. Samples were collected at week 12 (day 84): pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10 and 24 hours post-dose. |
| **Time Frame** | 12 weeks |
| **Safety Issue** | No |

**Population Description**

| **Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.** |
|---|
| All subjects with evaluable PK parameter data and no major protocol deviations with impact on PK data were included in the PK data analysis. |

**Reporting Groups**

| | Description |
|---|---|
| **Aliskiren** | In open label run-in phase (period 1), patients started with ramipril 2.5 mg or 5.0 mg capsule once daily (o.d) depending on previous treatment with RAAS blockers and up-titrated to ramipril 10 mg capsule o.d by end of period 1. In double blind phase (Period 2), patients received aliskiren (150 mg once daily) up titrated to 300 mg once daily after 1 week of treatment following a clinical safety patient assessment at the study site and matching placebo of ramipril capsules. |

**Measured Values**

| | Aliskiren |
|---|---|
| **Number of Participants Analyzed [units: participants]** | **40** |
| **Pharmacokinetic of Aliskiren: The Area Under the Plasma Concentration-time Curve From Time Zero to the Time of the Last Quantifiable Concentration (AUClast) [units: hr*ng/mL] Mean (Standard Deviation)** | **3041 (1669.1)** |

**No statistical analysis provided for Pharmacokinetic of Aliskiren: The Area Under the Plasma Concentration-time Curve From Time Zero to the Time of the Last Quantifiable Concentration (AUClast)**

10. Secondary: Pharmacokinetic of Aliskiren: The Area Under the Plasma Concentration-time Curve From Time Zero to Infinity (AUCinf) [ Time Frame: 12 weeks ]

| | |
|---|---|
| **Measure Type** | Secondary |
| **Measure Title** | Pharmacokinetic of Aliskiren: The Area Under the Plasma Concentration-time Curve From Time Zero to Infinity (AUCinf) |
| **Measure Description** | Blood samples (2 mL) for the determination of aliskiren concentration in plasma were collected using an indwelling cannula inserted in a forearm vein. Samples were collected at week 12 (day 84): pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10 and 24 hours post-dose. |
| **Time Frame** | 12 weeks |
| **Safety Issue** | No |

**Population Description**

| |
|---|
| **Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.** |
| All subjects with evaluable PK parameter data and no major protocol deviations with impact on PK data were included in the PK data analysis. |

**Reporting Groups**

| | **Description** |
|---|---|
| **Aliskiren** | In open label run-in phase (period 1), patients started with ramipril 2.5 mg or 5.0 mg capsule once daily (o.d) depending on previous treatment with RAAS blockers and up-titrated to ramipril 10 mg capsule o.d by end of period 1. In double blind phase (Period 2), patients received aliskiren (150 mg once daily) up titrated to 300 mg once daily after 1 week of treatment following a clinical safety patient assessment at the study site and matching placebo of ramipril capsules. |

**Measured Values**

| | **Aliskiren** |
|---|---|
| **Number of Participants Analyzed [units: participants]** | **19** |
| **Pharmacokinetic of Aliskiren: The Area Under the Plasma Concentration-time Curve From Time Zero to Infinity (AUCinf) [units: hr*ng/mL] Mean (Standard Deviation)** | **3502 (1907.5)** |

**No statistical analysis provided for Pharmacokinetic of Aliskiren: The Area Under the Plasma Concentration-time Curve From Time Zero to Infinity (AUCinf)**

11. Secondary: Pharmacokinetic of Aliskiren: The Terminal Elimination Half-life (T½) [ Time Frame: 12 weeks ]

| | |
|---|---|
| **Measure Type** | Secondary |
| **Measure Title** | Pharmacokinetic of Aliskiren: The Terminal Elimination Half-life (T½) |
| **Measure Description** | Blood samples (2 mL) for the determination of aliskiren concentration in plasma were collected using an indwelling cannula inserted in a forearm vein. Samples were collected at week 12 (day 84): pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10 and 24 hours post-dose. |
| **Time Frame** | 12 weeks |
| **Safety Issue** | No |

**Population Description**

| |
|---|
| **Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.** |
| All subjects with evaluable PK parameter data and no major protocol deviations with impact on PK data were included in the PK data analysis. |

**Reporting Groups**

| | **Description** |
|---|---|

| | |
|---|---|
| **Aliskiren** | In open label run-in phase (period 1), patients started with ramipril 2.5 mg or 5.0 mg capsule once daily (o.d) depending on previous treatment with RAAS blockers and up-titrated to ramipril 10 mg capsule o.d by end of period 1. In double blind phase (Period 2), patients received aliskiren (150 mg once daily) up titrated to 300 mg once daily after 1 week of treatment following a clinical safety patient assessment at the study site and matching placebo of ramipril capsules. |

**Measured Values**

| | Aliskiren |
|---|---|
| **Number of Participants Analyzed [units: participants]** | **19** |
| **Pharmacokinetic of Aliskiren: The Terminal Elimination Half-life (T½) [units: hour] Mean (Standard Deviation)** | **31.02 (10.624)** |

**No statistical analysis provided for Pharmacokinetic of Aliskiren: The Terminal Elimination Half-life (T½)**

## Serious Adverse Events

Hide Serious Adverse Events

| | |
|---|---|
| **Time Frame** | No text entered. |
| **Additional Description** | Reported adverse events summarized events of the run-in period and double blind period. All serious adverse (SAEs) events were not suspected to be related to study drug |

**Reporting Groups**

| | Description |
|---|---|
| **Ramipril** | In open label run-in phase (period 1), patients started with ramipril 2.5 mg or 5.0 mg capsule once daily (o.d) depending on previous treatment with RAAS blockers and up-titrated to ramipril 10 mg capsule o.d by end of period 1.<br>In double blind phase (Period 2), patients received ramipril 10 mg capsule o.d and matching placebo of aliskiren tablet. |
| **Aliskiren** | In open label run-in phase (period 1), patients started with ramipril 2.5 mg or 5.0 mg capsule once daily (o.d) depending on previous treatment with RAAS blockers and up-titrated to ramipril 10 mg capsule o.d by end of period 1. In double blind phase (Period 2), patients received aliskiren (150 mg once daily) up titrated to 300 mg once daily after 1 week of treatment following a clinical safety patient assessment at the study site and matching placebo of ramipril capsules. |
| **Ramipril + Aliskiren** | In open label run-in phase (period 1), patients started with ramipril 2.5 mg or 5.0 mg capsule once daily (o.d) depending on previous treatment with RAAS blockers and up-titrated to ramipril 10 mg capsule o.d by end of period 1.<br>In double blind phase (period 2), patients received ramipril (10 mg once daily capsule) and aliskiren (150 mg once daily tablet) up titrated to 300 mg once daily after 1 week of treatment following a clinical safety patient assessment at the study site. |

**Serious Adverse Events**

| | Ramipril | Aliskiren | Ramipril + Aliskiren |
|---|---|---|---|
| **Total, serious adverse events** | | | |
| **# participants affected / at risk** | **7/42 (16.67%)** | **2/40 (5.00%)** | **3/41 (7.32%)** |
| **Cardiac disorders** | | | |
| **Acute myocardial infarction † 1** | | | |
| **# participants affected / at risk** | **1/42 (2.38%)** | **0/40 (0.00%)** | **0/41 (0.00%)** |
| **Adams-Stokes syndrome † 1** | | | |
| **# participants affected / at risk** | **0/42 (0.00%)** | **0/40 (0.00%)** | **1/41 (2.44%)** |
| **Bradycardia † 1** | | | |
| **# participants affected / at risk** | **0/42 (0.00%)** | **0/40 (0.00%)** | **1/41 (2.44%)** |

| | | | |
|---|---|---|---|
| **Cardiac failure † 1** | | | |
| **# participants affected / at risk** | **4/42 (9.52%)** | **2/40 (5.00%)** | **0/41 (0.00%)** |
| **Cardiac failure chronic † 1** | | | |
| **# participants affected / at risk** | **1/42 (2.38%)** | **0/40 (0.00%)** | **0/41 (0.00%)** |
| **Myocardial infarction † 1** | | | |
| **# participants affected / at risk** | **0/42 (0.00%)** | **0/40 (0.00%)** | **1/41 (2.44%)** |
| **Gastrointestinal disorders** | | | |
| **Abdominal pain † 1** | | | |
| **# participants affected / at risk** | **0/42 (0.00%)** | **1/40 (2.50%)** | **0/41 (0.00%)** |
| **General disorders** | | | |
| **Sudden death † 1** | | | |
| **# participants affected / at risk** | **1/42 (2.38%)** | **0/40 (0.00%)** | **0/41 (0.00%)** |
| **Hepatobiliary disorders** | | | |
| **Cholecystitis † 1** | | | |
| **# participants affected / at risk** | **1/42 (2.38%)** | **0/40 (0.00%)** | **0/41 (0.00%)** |

† Events were collected by systematic assessment
1 Term from vocabulary, MedDRA

## Other Adverse Events

Hide Other Adverse Events

| | |
|---|---|
| **Time Frame** | No text entered. |
| **Additional Description** | Reported adverse events summarized events of the run-in period and double blind period. All serious adverse (SAEs) events were not suspected to be related to study drug |

**Frequency Threshold**

| | |
|---|---|
| **Threshold above which other adverse events are reported** | 5% |

**Reporting Groups**

| | **Description** |
|---|---|
| **Ramipril** | In open label run-in phase (period 1), patients started with ramipril 2.5 mg or 5.0 mg capsule once daily (o.d) depending on previous treatment with RAAS blockers and up-titrated to ramipril 10 mg capsule o.d by end of period 1.<br>In double blind phase (Period 2), patients received ramipril 10 mg capsule o.d and matching placebo of aliskiren tablet. |
| **Aliskiren** | In open label run-in phase (period 1), patients started with ramipril 2.5 mg or 5.0 mg capsule once daily (o.d) depending on previous treatment with RAAS blockers and up-titrated to ramipril 10 mg capsule o.d by end of period 1. In double blind phase (Period 2), patients received aliskiren (150 mg once daily) up titrated to 300 mg once daily after 1 week of treatment following a clinical safety patient assessment at the study site and matching placebo of ramipril capsules. |
| **Ramipril + Aliskiren** | In open label run-in phase (period 1), patients started with ramipril 2.5 mg or 5.0 mg capsule once daily (o.d) depending on previous treatment with RAAS blockers and up-titrated to ramipril 10 mg capsule o.d by end of period 1.<br>In double blind phase (period 2), patients received ramipril (10 mg once daily capsule) and aliskiren (150 mg once daily tablet) up titrated to 300 mg once daily after 1 week of treatment following a clinical safety patient assessment at the study site. |

**Other Adverse Events**

| | **Ramipril** | **Aliskiren** | **Ramipril + Aliskiren** |
|---|---|---|---|
| **Total, other (not including serious) adverse events** | | | |

| | | | |
|---|---|---|---|
| **# participants affected / at risk** | **6/42 (14.29%)** | **3/40 (7.50%)** | **7/41 (17.07%)** |
| **Cardiac disorders** | | | |
| **Tachycardia † 1** | | | |
| **# participants affected / at risk** | **0/42 (0.00%)** | **1/40 (2.50%)** | **5/41 (12.20%)** |
| **Infections and infestations** | | | |
| **Nasopharyngitis † 1** | | | |
| **# participants affected / at risk** | **2/42 (4.76%)** | **0/40 (0.00%)** | **3/41 (7.32%)** |
| **Investigations** | | | |
| **Electrocardiogram QT prolonged † 1** | | | |
| **# participants affected / at risk** | **4/42 (9.52%)** | **2/40 (5.00%)** | **1/41 (2.44%)** |

† Events were collected by systematic assessment
1 Term from vocabulary, MedDRA

## Limitations and Caveats

Hide Limitations and Caveats

| **Limitations of the study, such as early termination leading to small numbers of participants analyzed and technical problems with measurement leading to unreliable or uninterpretable data** |
|---|
| No text entered. |

## More Information

Hide More Information

**Certain Agreements:**

| |
|---|
| Principal Investigators are **NOT** employed by the organization sponsoring the study. |
| There **IS** an agreement between Principal Investigators and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed. |
| The agreement is:<br>☐ The only disclosure restriction on the PI is that the sponsor can review results communications prior to public release and can embargo communications regarding trial results for a period that is **less than or equal to 60 days**. The sponsor cannot require changes to the communication and cannot extend the embargo.<br>☐ The only disclosure restriction on the PI is that the sponsor can review results communications prior to public release and can embargo communications regarding trial results for a period that is **more than 60 days but less than or equal to 180 days**. The sponsor cannot require changes to the communication and cannot extend the embargo.<br>Other disclosure agreement that restricts the right of the PI to discuss or publish trial results after the trial is completed.<br>☑ **Restriction Description:** The terms and conditions of Novartis' agreements with its investigators may vary. However, Novartis does not prohibit any investigator from publishing. Any publications from a single-site are postponed until the publication of the pooled data (i.e., data from all sites) in the clinical trial or disclosure of trial results in their entirety. |

**Results Point of Contact:**

Name/Title: Study Director
Organization: Novartis Pharmaceuticals
phone: 862-778-8300

**No publications provided**

Responsible Party: Novartis ( Novartis Pharmaceuticals )

| | |
|---|---|
| ClinicalTrials.gov Identifier: | NCT00923156 History of Changes |
| Other Study ID Numbers: | **CSPP100A2252**<br>EudraCT 2008-001035-35 |
| Study First Received: | June 17, 2009 |
| Results First Received: | February 1, 2012 |
| Last Updated: | July 19, 2012 |
| Health Authority: | Russia: Ministry of Health of the Russian Federation<br>Poland: Ministry of Health<br>Germany: Federal Institute for Drugs and Medical Devices |