



Clinical trial results:

A randomized, multi-center, parallel group, double-blind, placebo and formoterol controlled 14 day dose ranging trial of 4 doses of indacaterol delivered via Twisthaler®, in adult and adolescent patients with persistent asthma

Due to a system error, the data reported in v1 is not correct and has been removed from public view.

Summary

| | |
|--------------------------|-------------------------|
| EudraCT number | 2007-003191-19 |
| Trial protocol | BE CZ ES HU GB PL SK DE |
| Global end of trial date | 18 April 2008 |

Results information

| | |
|--------------------------------|--|
| Result version number | v2 (current) |
| This version publication date | 08 July 2016 |
| First version publication date | 07 August 2015 |
| Version creation reason | <ul style="list-style-type: none">• Correction of full data set Corrected P-value in primary outcome measure for the comparison of Formoterol 12 µg v Indacaterol 500 µg |

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | CQMF149A2201 |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00545272 |
| 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) | No |
| 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? | Yes |

Notes:

Results analysis stage

| | |
|--|---------------|
| Analysis stage | Final |
| Date of interim/final analysis | 18 April 2008 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 18 April 2008 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial was to evaluate the dose response relationship among four doses of indacaterol treatment (62.5, 125, 250, and 500 micrograms [μg]) administered once daily (o.d.) and placebo as measured by the mean change from baseline to 24 hours (post-dose) trough forced expiratory volume (FEV1) after 14 days of treatment.

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.

Inhaled short acting β_2 -agonist (100 μg / 90 μg salbutamol/albuterol) metered dose inhaler (MDI) or dry powder inhaler (DPI) formulation was allowed as rescue medication. Subjects were instructed to abstain from taking rescue salbutamol/ albuterol within the 6 hours of the start of each visit unless absolutely necessary. The investigator provided follow-up medical care for all subjects who were prematurely withdrawn from the study, or referred them for appropriate ongoing care.

Background therapy:

Subjects who were using a long acting β_2 -agonist (LABA) prior screening were moved to short acting β_2 -agonists (SABA) treatment as needed. Subjects who were using fixed-dose combinations, used inhaled corticosteroid monotherapy in addition to SABA as needed as background therapy in the study.

Evidence for comparator:

Formoterol fumarate, an approved medication for the treatment of subjects with asthma was used as an active comparator group in this study. Subjects were required to use inhaled corticosteroid at the standard recommended dose (12 μg twice daily) for the duration of the study.

| | |
|---|-----------------|
| Actual start date of recruitment | 05 October 2007 |
| 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 | Poland: 82 |
| Country: Number of subjects enrolled | Slovakia: 11 |
| Country: Number of subjects enrolled | Spain: 7 |
| Country: Number of subjects enrolled | United Kingdom: 36 |
| Country: Number of subjects enrolled | Belgium: 61 |
| Country: Number of subjects enrolled | Czech Republic: 56 |

| | |
|--------------------------------------|------------------|
| Country: Number of subjects enrolled | Germany: 26 |
| Country: Number of subjects enrolled | Hungary: 40 |
| Country: Number of subjects enrolled | South Africa: 35 |
| Country: Number of subjects enrolled | Israel: 38 |
| Worldwide total number of subjects | 392 |
| EEA total number of subjects | 319 |

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) | 25 |
| Adults (18-64 years) | 332 |
| From 65 to 84 years | 35 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 49 centres in 10 countries.

Pre-assignment

Screening details:

A total of 583 subjects were screened, of which 392 subjects were randomized into the study.

Period 1

| | |
|------------------------------|--|
| Period 1 title | Double-blind Treatment Period (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Data analyst |

Blinding implementation details:

The identity of the active and placebo treatments was concealed by the use of study drugs that were all identical in packaging, labeling, schedule of administration and appearance. A double-dummy design was used because the inhalers required for the administration of active comparator and experimental treatments were different. Unblinding was allowed in the case of subject emergencies, and at the conclusion of the study.

Arms

| | |
|------------------------------|---------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Indacaterol 62.5 µg |

Arm description:

Subjects received indacaterol 62.5 µg o.d., and placebo to formoterol twice daily (b.i.d.) for 14 days.

| | |
|--|---------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Indacaterol |
| Investigational medicinal product code | QMF149 |
| Other name | |
| Pharmaceutical forms | Inhalation powder, hard capsule |
| Routes of administration | Inhalation use |

Dosage and administration details:

Indacaterol 62.5 µg was delivered by the Twisthaler device o.d. for 14 days

| | |
|--|---------------------------------|
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder, hard capsule |
| Routes of administration | Inhalation use |

Dosage and administration details:

Placebo to formoterol was delivered by the Aerolizer device b.i.d. for 14 days.

| | |
|------------------|--------------------|
| Arm title | Indacaterol 125 µg |
|------------------|--------------------|

Arm description:

Subjects received indacaterol 125 µg o.d., and placebo to formoterol twice daily for 14 days.

| | |
|--|---------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Indacaterol |
| Investigational medicinal product code | QMF149 |
| Other name | |
| Pharmaceutical forms | Inhalation powder, hard capsule |
| Routes of administration | Inhalation use |

| | |
|--|---------------------------------|
| Dosage and administration details: | |
| Indacaterol 125 µg was delivered by the Twisthaler device o.d. for 14 days | |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder, hard capsule |
| Routes of administration | Inhalation use |
| Dosage and administration details: | |
| Placebo to formoterol was delivered by the Aerolizer device twice daily for 14 days. | |
| Arm title | Indacaterol 250 µg |
| Arm description: | |
| Subjects received indacaterol 250 µg o.d., and placebo to formoterol b.i.d. for 14 days. | |
| Arm type | Experimental |
| Investigational medicinal product name | Indacaterol |
| Investigational medicinal product code | QMF149 |
| Other name | |
| Pharmaceutical forms | Inhalation powder, hard capsule |
| Routes of administration | Inhalation use |
| Dosage and administration details: | |
| Indacaterol 250 µg was delivered by the Twisthaler device o.d. for 14 days | |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder, hard capsule |
| Routes of administration | Inhalation use |
| Dosage and administration details: | |
| Placebo to formoterol was delivered by the Aerolizer device b.i.d. for 14 days. | |
| Arm title | Indacaterol 500 µg |
| Arm description: | |
| Subjects received indacaterol 500 µg o.d., and placebo to formoterol b.i.d. for 14 days. | |
| Arm type | Experimental |
| Investigational medicinal product name | Indacaterol |
| Investigational medicinal product code | QMF149 |
| Other name | |
| Pharmaceutical forms | Inhalation powder, hard capsule |
| Routes of administration | Inhalation use |
| Dosage and administration details: | |
| Indacaterol 500 µg was delivered by the Twisthaler device o.d. for 14 days | |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder, hard capsule |
| Routes of administration | Inhalation use |
| Dosage and administration details: | |
| Placebo to formoterol was delivered by the Aerolizer device b.i.d. for 14 days. | |
| Arm title | Formoterol 12 µg |
| Arm description: | |
| Subjects received formoterol 12 µg b.i.d., and placebo to indacaterol o.d. for 14 days. | |
| Arm type | Active comparator |

| | |
|---|---------------------------------|
| Investigational medicinal product name | Formoterol |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder, hard capsule |
| Routes of administration | Inhalation use |
| Dosage and administration details: | |
| Formoterol 12 µg was delivered by the Aerolizer device b.i.d. for 14 days. | |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder, hard capsule |
| Routes of administration | Inhalation use |
| Dosage and administration details: | |
| Placebo to indacaterol was delivered by the Twisthaler device o.d. for 14 days. | |
| Arm title | Placebo |
| Arm description: | |
| Subjects received placebo to indacaterol o.d., and placebo to formoterol twice daily for 14 days. | |
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder, hard capsule |
| Routes of administration | Inhalation use |
| Dosage and administration details: | |
| Placebo to indacaterol was delivered by the Twisthaler device o.d. for 14 days. | |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder, hard capsule |
| Routes of administration | Inhalation use |
| Dosage and administration details: | |
| Placebo to formoterol was delivered by the Aerolizer device b.i.d. for 14 days. | |

| Number of subjects in period 1 | Indacaterol 62.5 µg | Indacaterol 125 µg | Indacaterol 250 µg |
|---------------------------------------|---------------------|--------------------|--------------------|
| Started | 61 | 68 | 65 |
| Completed | 61 | 67 | 64 |
| Not completed | 0 | 1 | 1 |
| Adverse event, non-fatal | - | - | 1 |
| Abnormal laboratory value | - | - | - |
| Lost to follow-up | - | - | - |
| Abnormal test procedure result | - | - | - |
| Protocol deviation | - | 1 | - |

| Number of subjects in period 1 | Indacaterol 500 µg | Formoterol 12 µg | Placebo |
|---------------------------------------|--------------------|------------------|---------|
| Started | 72 | 64 | 62 |

| | | | |
|--------------------------------|----|----|----|
| Completed | 71 | 62 | 59 |
| Not completed | 1 | 2 | 3 |
| Adverse event, non-fatal | - | - | 1 |
| Abnormal laboratory value | - | - | 1 |
| Lost to follow-up | - | 1 | - |
| Abnormal test procedure result | - | 1 | - |
| Protocol deviation | 1 | - | 1 |

Baseline characteristics

Reporting groups

| | |
|---|---------------------|
| Reporting group title | Indacaterol 62.5 µg |
| Reporting group description: | |
| Subjects received indacaterol 62.5 µg o.d., and placebo to formoterol twice daily (b.i.d.) for 14 days. | |
| Reporting group title | Indacaterol 125 µg |
| Reporting group description: | |
| Subjects received indacaterol 125 µg o.d., and placebo to formoterol twice daily for 14 days. | |
| Reporting group title | Indacaterol 250 µg |
| Reporting group description: | |
| Subjects received indacaterol 250 µg o.d., and placebo to formoterol b.i.d. for 14 days. | |
| Reporting group title | Indacaterol 500 µg |
| Reporting group description: | |
| Subjects received indacaterol 500 µg o.d., and placebo to formoterol b.i.d. for 14 days. | |
| Reporting group title | Formoterol 12 µg |
| Reporting group description: | |
| Subjects received formoterol 12 µg b.i.d., and placebo to indacaterol o.d. for 14 days. | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Subjects received placebo to indacaterol o.d., and placebo to formoterol twice daily for 14 days. | |

| Reporting group values | Indacaterol 62.5 µg | Indacaterol 125 µg | Indacaterol 250 µg |
|---------------------------|---------------------|--------------------|--------------------|
| Number of subjects | 61 | 68 | 65 |
| Age categorical | | | |
| Units: Subjects | | | |
| Adolescents (12-17 years) | | | |
| Adults (18-64 years) | | | |
| From 65-84 years | | | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 41.3 | 38.4 | 36.6 |
| standard deviation | ± 16.27 | ± 17.25 | ± 15.76 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 28 | 37 | 36 |
| Male | 33 | 31 | 29 |

| Reporting group values | Indacaterol 500 µg | Formoterol 12 µg | Placebo |
|---------------------------|--------------------|------------------|---------|
| Number of subjects | 72 | 64 | 62 |
| Age categorical | | | |
| Units: Subjects | | | |
| Adolescents (12-17 years) | | | |
| Adults (18-64 years) | | | |
| From 65-84 years | | | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 40.1 | 44 | 39.8 |
| standard deviation | ± 15.47 | ± 17.98 | ± 15.82 |

| | | | |
|---------------------------------------|----|----|----|
| Gender categorical Units: Subjects | | | |
| Female | 39 | 27 | 37 |
| Male | 33 | 37 | 25 |

| | | | |
|---|-------|--|--|
| Reporting group values | Total | | |
| Number of subjects | 392 | | |
| Age categorical Units: Subjects | | | |
| Adolescents (12-17 years) | 0 | | |
| Adults (18-64 years) | 0 | | |
| From 65-84 years | 0 | | |
| Age continuous Units: years arithmetic mean standard deviation | - | | |
| Gender categorical Units: Subjects | | | |
| Female | 204 | | |
| Male | 188 | | |

End points

End points reporting groups

| | |
|---|---------------------|
| Reporting group title | Indacaterol 62.5 µg |
| Reporting group description: Subjects received indacaterol 62.5 µg o.d., and placebo to formoterol twice daily (b.i.d.) for 14 days. | |
| Reporting group title | Indacaterol 125 µg |
| Reporting group description: Subjects received indacaterol 125 µg o.d., and placebo to formoterol twice daily for 14 days. | |
| Reporting group title | Indacaterol 250 µg |
| Reporting group description: Subjects received indacaterol 250 µg o.d., and placebo to formoterol b.i.d. for 14 days. | |
| Reporting group title | Indacaterol 500 µg |
| Reporting group description: Subjects received indacaterol 500 µg o.d., and placebo to formoterol b.i.d. for 14 days. | |
| Reporting group title | Formoterol 12 µg |
| Reporting group description: Subjects received formoterol 12 µg b.i.d., and placebo to indacaterol o.d. for 14 days. | |
| Reporting group title | Placebo |
| Reporting group description: Subjects received placebo to indacaterol o.d., and placebo to formoterol twice daily for 14 days. | |

Primary: Change from baseline in trough forced expiratory volume in 1 second (FEV1) at Day 14

| | |
|---|--|
| End point title | Change from baseline in trough forced expiratory volume in 1 second (FEV1) at Day 14 |
| End point description: The FEV1 is the amount of air which can be forcibly exhaled from the lungs in the first second of a forced exhalation. Baseline FEV1 was defined as the average of two FEV1 assessments taken at 50 minutes and 15 minutes before the first study drug administration. Trough FEV1 was defined as the mean of 2 FEV1 measurements at 23 hour 10 minutes and 23 hours 45 minutes post-dose. If one of these assessments was missing then the trough was equal to the non-missing assessment. Positive change from baseline in trough favored experimental treatment. The analysis was performed in Intent to treat (ITT) population, defined as all randomized subjects who had a baseline and at least one post-dose measurement. | |
| End point type | Primary |
| End point timeframe: Day 1 Baseline (prior to first dose), Day 15 (24 hours after last dose) | |

| End point values | Indacaterol 62.5 µg | Indacaterol 125 µg | Indacaterol 250 µg | Indacaterol 500 µg |
|-------------------------------------|---------------------|--------------------|--------------------|--------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 60 | 67 | 63 | 68 |
| Units: litres (L) | | | | |
| least squares mean (standard error) | 0.039 (± 0.0408) | 0.054 (± 0.0383) | 0.124 (± 0.0401) | 0.166 (± 0.0381) |

| End point values | Formoterol 12 µg | Placebo | | |
|-------------------------------------|------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 62 | 58 | | |
| Units: litres (L) | | | | |
| least squares mean (standard error) | 0.075 (± 0.0405) | -0.018 (± 0.0415) | | |

Statistical analyses

| Statistical analysis title | Change in trough FEV1 (Indacaterol versus Placebo) |
|---|--|
| Statistical analysis description: | |
| Change from baseline to (24 hour post dose) trough FEV1 (L) was analyzed using Analysis of Covariance ANCOVA adjusting for treatment and region with baseline FEV1 as a covariate | |
| Comparison groups | Placebo v Indacaterol 62.5 µg |
| Number of subjects included in analysis | 118 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0298 ^[1] |
| Method | ANCOVA |
| Parameter estimate | Least Square Mean Difference |
| Point estimate | 0.057 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.051 |
| upper limit | 0.165 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.0547 |

Notes:

[1] - p-value was not adjusted for multiplicity.

| Statistical analysis title | Change in trough FEV1 (Indacaterol versus Placebo) |
|---|--|
| Statistical analysis description: | |
| Change from baseline to (24 hour post dose) trough FEV1 (L) was analyzed using Analysis of Covariance ANCOVA adjusting for treatment and region with baseline FEV1 as a covariate | |
| Comparison groups | Placebo v Indacaterol 125 µg |
| Number of subjects included in analysis | 125 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.176 ^[2] |
| Method | ANCOVA |
| Parameter estimate | Least Square Mean Difference |
| Point estimate | 0.072 |

| | |
|----------------------|----------------------------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.033 |
| upper limit | 0.177 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.0533 |

Notes:

[2] - p-value was not adjusted for multiplicity.

| | |
|-----------------------------------|--|
| Statistical analysis title | Change in trough FEV1 (Indacaterol versus Placebo) |
|-----------------------------------|--|

Statistical analysis description:

Change from baseline to (24 hour post dose) trough FEV1 (L) was analyzed using Analysis of Covariance ANCOVA adjusting for treatment and region with baseline FEV1 as a covariate

| | |
|---|------------------------------|
| Comparison groups | Placebo v Indacaterol 250 µg |
| Number of subjects included in analysis | 121 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.009 ^[3] |
| Method | ANCOVA |
| Parameter estimate | Least Square Mean Difference |
| Point estimate | 0.142 |

Confidence interval

| | |
|----------------------|----------------------------|
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.036 |
| upper limit | 0.248 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.0541 |

Notes:

[3] - p-value was not adjusted for multiplicity.

| | |
|-----------------------------------|--|
| Statistical analysis title | Change in trough FEV1 (Indacaterol versus Placebo) |
|-----------------------------------|--|

Statistical analysis description:

Change from baseline to (24 hour post dose) trough FEV1 (L) was analyzed using Analysis of Covariance ANCOVA adjusting for treatment and region with baseline FEV1 as a covariate

| | |
|---|------------------------------|
| Comparison groups | Placebo v Indacaterol 500 µg |
| Number of subjects included in analysis | 126 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[4] |
| Method | ANCOVA |
| Parameter estimate | Least Square Mean Difference |
| Point estimate | 0.184 |

Confidence interval

| | |
|----------------------|----------------------------|
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.08 |
| upper limit | 0.289 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.0531 |

Notes:

[4] - p-value was not adjusted for multiplicity.

| | |
|--|--|
| Statistical analysis title | Change in trough FEV1 (Indacaterol versus Placebo) |
| Statistical analysis description: Change from baseline to (24 hour post dose) trough FEV1 (L) was analyzed using Analysis of Covariance ANCOVA adjusting for treatment and region with baseline FEV1 as a covariate | |
| Comparison groups | Placebo v Formoterol 12 µg |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.086 ^[5] |
| Method | ANCOVA |
| Parameter estimate | Least Square Mean Difference |
| Point estimate | 0.093 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.013 |
| upper limit | 0.2 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.0543 |

Notes:

[5] - p-value was not adjusted for multiplicity.

| | |
|--|---|
| Statistical analysis title | Change in trough FEV1 (Indacaterol vs formoterol) |
| Statistical analysis description: Change from baseline to (24 hour post dose) trough FEV1 (L) was analyzed using Analysis of Covariance ANCOVA adjusting for treatment and region with baseline FEV1 as a covariate | |
| Comparison groups | Indacaterol 62.5 µg v Formoterol 12 µg |
| Number of subjects included in analysis | 122 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | = 0.499 ^[6] |
| Method | ANCOVA |
| Parameter estimate | Least Square Mean Difference |
| Point estimate | -0.036 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.142 |
| upper limit | 0.07 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.0539 |

Notes:

[6] - p-value was not adjusted for multiplicity.

| | |
|--|---|
| Statistical analysis title | Change in trough FEV1 (Indacaterol vs formoterol) |
| Statistical analysis description: Change from baseline to (24 hour post dose) trough FEV1 (L) was analyzed using Analysis of Covariance ANCOVA adjusting for treatment and region with baseline FEV1 as a covariate | |

| | |
|---|---------------------------------------|
| Comparison groups | Formoterol 12 µg v Indacaterol 125 µg |
| Number of subjects included in analysis | 129 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | = 0.687 ^[7] |
| Method | ANCOVA |
| Parameter estimate | Least Square Mean Difference |
| Point estimate | -0.021 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.124 |
| upper limit | 0.082 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.0524 |

Notes:

[7] - p-value was not adjusted for multiplicity.

| | |
|---|---|
| Statistical analysis title | Change in trough FEV1 (Indacaterol vs formoterol) |
| Statistical analysis description: | |
| Change from baseline to (24 hour post dose) trough FEV1 (L) was analyzed using Analysis of Covariance ANCOVA adjusting for treatment and region with baseline FEV1 as a covariate | |
| Comparison groups | Formoterol 12 µg v Indacaterol 250 µg |
| Number of subjects included in analysis | 125 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | = 0.362 ^[8] |
| Method | ANCOVA |
| Parameter estimate | Least Square Mean Difference |
| Point estimate | 0.049 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.056 |
| upper limit | 0.153 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.0532 |

Notes:

[8] - p-value was not adjusted for multiplicity.

| | |
|---|---|
| Statistical analysis title | Change in trough FEV1 (Indacaterol vs formoterol) |
| Statistical analysis description: | |
| Change from baseline to (24 hour post dose) trough FEV1 (L) was analyzed using Analysis of Covariance ANCOVA adjusting for treatment and region with baseline FEV1 as a covariate | |
| Comparison groups | Formoterol 12 µg v Indacaterol 500 µg |

| | |
|---|------------------------------|
| Number of subjects included in analysis | 130 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | = 0.082 ^[9] |
| Method | ANCOVA |
| Parameter estimate | Least Square Mean Difference |
| Point estimate | 0.091 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.012 |
| upper limit | 0.194 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.0523 |

Notes:

[9] - p-value was not adjusted for multiplicity.

Secondary: Change from baseline in trough forced expiratory volume in 1 second (FEV1) at Day 1

| | |
|-----------------|---|
| End point title | Change from baseline in trough forced expiratory volume in 1 second (FEV1) at Day 1 |
|-----------------|---|

End point description:

The FEV1 is the amount of air which can be forcibly exhaled from the lungs in the first second of a forced exhalation. Baseline FEV1 was defined as the average of two FEV1 assessments taken at 50 minutes and 15 minutes before the first study drug administration. Trough FEV1 was defined as the mean of 2 FEV1 measurements at 23 hour 10 minutes and 23 hours 45 minutes post-dose. If one of these assessments was missing then the trough was equal to the non-missing assessment. Positive change from baseline in trough favored experimental treatment. The analysis was performed in ITT population.

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

End point timeframe:

Day 1 baseline (prior to first-dose), Day 1 (24 hours post first-dose)

| End point values | Indacaterol 62.5 µg | Indacaterol 125 µg | Indacaterol 250 µg | Indacaterol 500 µg |
|-------------------------------------|------------------------|-----------------------|-----------------------|-----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 61 | 68 | 64 | 69 |
| Units: Litres | | | | |
| least squares mean (standard error) | 0.054 (± 0.0347) | 0.081 (± 0.0326) | 0.143 (± 0.0339) | 0.141 (± 0.0326) |

| End point values | Formoterol 12 µg | Placebo | | |
|-------------------------------------|---------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 63 | 62 | | |
| Units: Litres | | | | |
| least squares mean (standard error) | 0.155 (± 0.0341) | 0.01 (± 0.0344) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Peak Forced Expiratory Volume in 1 Second (FEV1) on Day 1 and Day 14

| | |
|-----------------|--|
| End point title | Time to Peak Forced Expiratory Volume in 1 Second (FEV1) on Day 1 and Day 14 |
|-----------------|--|

End point description:

FEV1 is the amount of air which can be forcibly exhaled from the lungs in the first second of a forced exhalation. Time to peak FEV1 was calculated in minutes from the time of inhalation of study drug to the time of the peak FEV1, which is taken as the maximum FEV1 recorded post-dose. The analysis was performed in the ITT population.

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

End point timeframe:

Day 1 and Day 14 (pre-dose and up to 4 hours post-dose)

| End point values | Indacaterol 62.5 µg | Indacaterol 125 µg | Indacaterol 250 µg | Indacaterol 500 µg |
|--------------------------------------|------------------------|-----------------------|-----------------------|-----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 61 | 68 | 65 | 72 |
| Units: minutes | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 1 (n= 61, 68, 65, 71, 64, 62) | 91 (± 83.02) | 109.6 (± 81.09) | 119 (± 81.64) | 116.2 (± 75.5) |
| Day 14 (n=61, 66, 64, 70, 62, 59) | 103.8 (± 86.67) | 118.7 (± 88.42) | 96.7 (± 70.65) | 114 (± 76.41) |

| End point values | Formoterol 12 µg | Placebo | | |
|--------------------------------------|---------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 64 | 62 | | |
| Units: minutes | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 1 (n= 61, 68, 65, 71, 64, 62) | 105.6 (± 70.64) | 90.5 (± 82.46) | | |
| Day 14 (n=61, 66, 64, 70, 62, 59) | 114.6 (± 71.64) | 80.4 (± 76.92) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Forced Expiratory Volume in 1 Second (FEV1) area under the curve from baseline to 4 hours post-dose (AUC 0-4) on Day 1 and Day 14

| | |
|-----------------|---|
| End point title | Forced Expiratory Volume in 1 Second (FEV1) area under the curve from baseline to 4 hours post-dose (AUC 0-4) on Day 1 and Day 14 |
|-----------------|---|

End point description:

FEV1 is the amount of air which can be forcibly exhaled from the lungs in the first second of a forced exhalation. FEV1 AUC (0-4) was evaluated for subjects with complete or incomplete FEV1 assessments, based on the observed FEV1 measurements. The missing FEV1 measurements were not interpolated. The analyses was performed in ITT population and accounted all subjects with at least one FEV1 assessment between baseline (pre-dose) and 4 hours post-dose. Here 'n' signifies those subjects evaluable for the outcome measure, at specified time-points, respectively.

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

End point timeframe:

Day 1 and Day 14 (pre-dose, 5, 20 and 30 minutes, 1, 2, 3, and 4 hours post-dose)

| End point values | Indacaterol 62.5 µg | Indacaterol 125 µg | Indacaterol 250 µg | Indacaterol 500 µg |
|-------------------------------------|------------------------|-----------------------|-----------------------|-----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 61 | 68 | 65 | 72 |
| Units: Litres | | | | |
| least squares mean (standard error) | | | | |
| Day 1 (n=61, 68, 65, 71, 64, 62) | 2.668 (± 0.0281) | 2.687 (± 0.0264) | 2.726 (± 0.0272) | 2.753 (± 0.0259) |
| Day 14 (n=61, 66, 64, 69, 62, 59) | 2.67 (± 0.0419) | 2.698 (± 0.04) | 2.772 (± 0.0411) | 2.786 (± 0.0393) |

| End point values | Formoterol 12 µg | Placebo | | |
|-------------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 64 | 62 | | |
| Units: Litres | | | | |
| least squares mean (standard error) | | | | |
| Day 1 (n=61, 68, 65, 71, 64, 62) | 2.832 (± 0.0274) | 2.547 (± 0.0279) | | |
| Day 14 (n=61, 66, 64, 69, 62, 59) | 2.821 (± 0.0418) | 2.565 (± 0.0426) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Morning and Evening Peak Expiratory Flow at Day 14

| | |
|---|--|
| End point title | Change From Baseline in Morning and Evening Peak Expiratory Flow at Day 14 |
| End point description: | |
| The Peak Expiratory Flow (PEF) is a convenient for monitoring of airway function at home, and it is commonly used to assess response to treatment or to document diurnal variation. PEF rate is the maximal rate that a person can exhale during a short maximal expiratory effort after fully inhaling. The PEF was measured using a peak flow meter every morning and evening during the study, prior administration of study medication, except evenings on the day of clinic visits. Change from baseline was the difference between the mean baseline PEF recorded during the screening period until the first day of treatment, and the overall mean PEF from Day 1 to 14. The analysis was performed in ITT population. Here 'n' signifies those subjects evaluable for this measure at specified time-points, respectively. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline (screening period), Day 1 up to Day 14 (treatment period) | |

| End point values | Indacaterol 62.5 µg | Indacaterol 125 µg | Indacaterol 250 µg | Indacaterol 500 µg |
|--|------------------------|-----------------------|-----------------------|-----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 61 | 68 | 65 | 72 |
| Units: Litres/minute | | | | |
| arithmetic mean (standard deviation) | | | | |
| Morning PEF (n=56, 61, 53, 63, 57, 48) | 18.7 (± 29.28) | 17.2 (± 34.07) | 25.7 (± 38.37) | 25.8 (± 47.36) |
| Evening PEF (n=56, 58, 54, 59, 55, 47) | 5.9 (± 36.92) | 4.2 (± 37.82) | 18.4 (± 36.7) | 25.8 (± 38.07) |

| End point values | Formoterol 12 µg | Placebo | | |
|--|---------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 64 | 62 | | |
| Units: Litres/minute | | | | |
| arithmetic mean (standard deviation) | | | | |
| Morning PEF (n=56, 61, 53, 63, 57, 48) | 25.2 (± 38.28) | -4.3 (± 43) | | |
| Evening PEF (n=56, 58, 54, 59, 55, 47) | 26.2 (± 35.01) | -11.4 (± 50.73) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects using rescue medication during day and night

| | |
|--|---|
| End point title | Number of subjects using rescue medication during day and night |
| End point description: | |
| Subjects recorded the use of rescue medications (salbutamol/albuterol) for treatment of asthma symptoms in a diary during day and night. Rescue medication during the day time was defined as number of puffs of rescue medication used in the 6 hours prior to evening PEF measurement. Rescue medication during the night time was defined as number of puffs of rescue medication used in the 12 hours prior recording the morning PEF measurement. The analysis was performed in ITT population. | |
| End point type | Secondary |

End point timeframe:

Day 1 up to Day 14

| End point values | Indacaterol 62.5 µg | Indacaterol 125 µg | Indacaterol 250 µg | Indacaterol 500 µg |
|-----------------------------|------------------------|-----------------------|-----------------------|-----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 61 | 68 | 65 | 72 |
| Units: Subjects | | | | |
| number (not applicable) | | | | |
| Day | 33 | 43 | 28 | 35 |
| Night | 36 | 40 | 36 | 34 |

| End point values | Formoterol 12 µg | Placebo | | |
|-----------------------------|---------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 64 | 62 | | |
| Units: Subjects | | | | |
| number (not applicable) | | | | |
| Day | 30 | 39 | | |
| Night | 31 | 40 | | |

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 are reported in this record from 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 | Indacaterol 62.5 µg |
|-----------------------|---------------------|

Reporting group description:

Indacaterol 62.5 µg

| | |
|-----------------------|--------------------|
| Reporting group title | Indacaterol 125 µg |
|-----------------------|--------------------|

Reporting group description:

Indacaterol 125 µg

| | |
|-----------------------|--------------------|
| Reporting group title | Indacaterol 250 µg |
|-----------------------|--------------------|

Reporting group description:

Indacaterol 250 µg

| | |
|-----------------------|--------------------|
| Reporting group title | Indacaterol 500 µg |
|-----------------------|--------------------|

Reporting group description:

Indacaterol 500 µg

| | |
|-----------------------|------------------|
| Reporting group title | Formoterol 12 µg |
|-----------------------|------------------|

Reporting group description:

Formoterol 12 µg

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Placebo

| Serious adverse events | Indacaterol 62.5 µg | Indacaterol 125 µg | Indacaterol 250 µg |
|---|---------------------|--------------------|--------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 68 (0.00%) | 0 / 65 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthmatic crisis | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 68 (0.00%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | Indacaterol 500 µg | Formoterol 12 µg | Placebo |
|------------------------------------|--------------------|------------------|---------|
| Total subjects affected by serious | | | |

| | | | |
|---|----------------|----------------|----------------|
| adverse events | | | |
| subjects affected / exposed | 0 / 72 (0.00%) | 0 / 64 (0.00%) | 1 / 62 (1.61%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthmatic crisis | | | |
| subjects affected / exposed | 0 / 72 (0.00%) | 0 / 64 (0.00%) | 1 / 62 (1.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

Frequency threshold for reporting non-serious adverse events: 2 %

| Non-serious adverse events | Indacaterol 62.5 µg | Indacaterol 125 µg | Indacaterol 250 µg |
|---|---------------------|--------------------|--------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 4 / 61 (6.56%) | 6 / 68 (8.82%) | 8 / 65 (12.31%) |
| Nervous system disorders | | | |
| Dysgeusia | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 68 (0.00%) | 0 / 65 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Headache | | | |
| subjects affected / exposed | 2 / 61 (3.28%) | 1 / 68 (1.47%) | 2 / 65 (3.08%) |
| occurrences (all) | 2 | 1 | 2 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 2 / 61 (3.28%) | 2 / 68 (2.94%) | 4 / 65 (6.15%) |
| occurrences (all) | 2 | 2 | 4 |
| Skin and subcutaneous tissue disorders | | | |
| Pruritus | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 2 / 68 (2.94%) | 0 / 65 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 68 (1.47%) | 2 / 65 (3.08%) |
| occurrences (all) | 0 | 1 | 2 |

| Non-serious adverse events | Indacaterol 500 µg | Formoterol 12 µg | Placebo |
|---|--------------------|------------------|---------|
| Total subjects affected by non-serious adverse events | | | |

| subjects affected / exposed | 14 / 72 (19.44%) | 3 / 64 (4.69%) | 3 / 62 (4.84%) |
|---|------------------|----------------|----------------|
| Nervous system disorders | | | |
| Dysgeusia | | | |
| subjects affected / exposed | 2 / 72 (2.78%) | 0 / 64 (0.00%) | 0 / 62 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Headache | | | |
| subjects affected / exposed | 2 / 72 (2.78%) | 2 / 64 (3.13%) | 2 / 62 (3.23%) |
| occurrences (all) | 2 | 2 | 2 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 8 / 72 (11.11%) | 0 / 64 (0.00%) | 1 / 62 (1.61%) |
| occurrences (all) | 8 | 0 | 1 |
| Skin and subcutaneous tissue disorders | | | |
| Pruritus | | | |
| subjects affected / exposed | 1 / 72 (1.39%) | 0 / 64 (0.00%) | 0 / 62 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 1 / 72 (1.39%) | 1 / 64 (1.56%) | 0 / 62 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|--------------|---|
| 31 July 2007 | The protocol was amended for compliance with national regulations or clinical practice concerning the inclusion of subjects less than 18 years of age in clinical trials and time frame for collection of AEs was modified to start after administration of first dose of study treatments. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported