

**Clinical trial results:****A SINGLE-DOSE, UNCONTROLLED, OPEN LABEL, NON-RANDOMIZED, CLINICAL PHARMACOLOGY STUDY OF CHF 5993 100/6/12.5 g PMDI (FIXED COMBINATION OF BECLOMETASONE DIPROPIONATE PLUS FORMOTEROL FUMARATE PLUS GLYCOPYRRONIUM BROMIDE) IN ASTHMATIC ADOLESCENT PATIENTS AND ADULT PATIENTS****Summary**

| | |
|--------------------------|------------------|
| EudraCT number | 2019-002238-35 |
| Trial protocol | PL |
| Global end of trial date | 04 February 2021 |

Results information

| | |
|--------------------------------|---|
| Result version number | v2 (current) |
| This version publication date | 12 November 2021 |
| First version publication date | 18 August 2021 |
| Version creation reason | • Correction of full data set Correction of the Paediatric regulatory details. |

Trial information**Trial identification**

| | |
|-----------------------|-----------------|
| Sponsor protocol code | CLI-05993CB1-01 |
|-----------------------|-----------------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Chiesi Farmaceutici S.p.A |
| Sponsor organisation address | Via Palermo 26/A, Parma, Italy, |
| Public contact | Clinical Trial Trasparenzy, Chiesi Farmaceutici S.p.A, clinicaltrials_info@chiesi.com |
| Scientific contact | Clinical Trial Trasparenzy, Chiesi Farmaceutici S.p.A, clinicaltrials_info@chiesi.com |

Notes:

Paediatric regulatory details

| | |
|--|---------------------|
| Is trial part of an agreed paediatric investigation plan (PIP) | Yes |
| EMA paediatric investigation plan number(s) | EMA-001875-PIP02-18 |
| 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 | 23 July 2021 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 04 February 2021 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To evaluate the systemic exposure to beclometasone 17-monopropionate (B17MP, active metabolite of beclometasone dipropionate [BDP]), formoterol, and glycopyrronium bromide [GB] as measured by the area under the plasma concentration-time curve (AUC) from 0 to the last quantifiable concentration (AUC_{0-t}, index of total systemic exposure) after inhalation of CHF 5993 pressurised metered-dose inhaler (pMDI) in adolescent asthmatic patients in comparison to adult asthmatic patients.

Protection of trial subjects:

This study was conducted in compliance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6 Good Clinical Practices (GCP) guidelines, the Declaration of Helsinki (1964 and amendments) and other local regulations as applicable.

The informed consent has been written separately in a language understandable to the adult and adolescent patients and/or patient's legal representative (where applicable).

Written informed consent was obtained by the Investigator from each patient or from the patient's legal representative prior to any study related procedures taking place by using the latest EC/IRB approved version of the document.

Background therapy:

CHF 5993 100/6/12.5 µg/actuation is an extra-fine fixed combination of an Inhaled corticosteroids (ICS), a Long-acting β₂-agonist (LABA) and a long-acting muscarinic antagonist (LAMA) containing Beclometasone Dipropionate (BDP) 100 µg/actuation plus Formoterol Fumarate (FF) 6 µg/actuation plus Glycopyrronium Bromide (GB) 12.5 µg/actuation has been developed as a hydrofluoroalkane (HFA) pressurised metered-dose inhaler (pMDI).

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 27 February 2020 |
| 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: 80 |
| Worldwide total number of subjects | 80 |
| EEA total number of subjects | 80 |

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) | 40 |
| Adults (18-64 years) | 40 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

A total of 82 asthmatic subjects divided into two age groups (41 adolescents and 41 adults) were screened, of which 80 were enrolled and treated (40 adolescents and 40 adults) and 2 subjects (1 adolescent and 1 adult) who failed screening.

Pre-assignment

Screening details:

Screening was performed from 28 to 21 days prior to the first administration of the study drug and the patient had been fasting for at least 10 hours, without smoking or nicotine-containing and had not engaged in strenuous activity in the 24 hours before the visit. The inclusion/exclusion criteria were assessed and there were 2 screening failures.

Pre-assignment period milestones

| | |
|------------------------------|-------------------|
| Number of subjects started | 82 ^[1] |
| Number of subjects completed | 80 |

Pre-assignment subject non-completion reasons

| | |
|----------------------------|---|
| Reason: Number of subjects | failure to meet Randomization Criteria: 1 |
| Reason: Number of subjects | patient and parent's fear for COVID-19: 1 |

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: According to the protocol 40 adolescent asthmatic patients (for an outcome of 37 evaluable patients) and 40 adult asthmatic patients (for an outcome of 37 evaluable patients) were planned to be enrolled. To reach a target, a total of 41 adolescent patients and 41 adult patients were screened, of whom 1 adolescent patient and 1 adult patient were screening failures. Therefore 40 adolescent patients and 40 adult patients were enrolled and received the study drug.

Period 1

| | |
|------------------------------|-----------------------------------|
| Period 1 title | Treatment Period (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|---------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Adolescents (12-17 years) |

Arm description:

Adolescent asthmatic patients who have received one single-dose (consisting of 4 inhalation) of fixed combination CHF 5993 400/24/50 µg pMDI (400 µg BDP, 24 µg FF, and 50 µg GB).

| | |
|--|----------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | CHF 5993 pMDI (100/6/12.5 µg) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Pressurised inhalation, solution |
| Routes of administration | Inhalation use |

Dosage and administration details:

Test product: CHF 5993 100/6/12.5 µg (BDP/FF/GB 100/6/12.5 µg per actuation) pMDI, fixed-dose combination of beclometasone dipropionate (BDP) + formoterol fumarate (FF) + glycopyrronium bromide (GB). The study medication was administered at clinical site on Day 1 as single dose by inhalation (4 inhalation in total) using the pMDI device, for a total dose of BDP 400 µg, FF 24 µg, GB 50 µg. The subjects were trained to use the pMDI device with (Aerosol Inhalation Monitor) AIM[™] Vitalograph® at the screening visit and at pre-dose on Day 1. The subjects were trained also using the pMDI placebo devices at screening and at Day 1.

| | |
|--|----------------------------------|
| Arm title | Adults (18-64 years) |
| Arm description: | |
| Adult asthmatic patients who have received one single-dose (consisting of 4 inhalation) of fixed combination CHF 5993 400/24/50 µg pMDI (400 µg BDP, 24 µg FF, and 50 µg GB) | |
| Arm type | Experimental |
| Investigational medicinal product name | CHF 5993 pMDI (100/6/12.5 µg) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Pressurised inhalation, solution |
| Routes of administration | Inhalation use |

Dosage and administration details:

Test product: CHF 5993 100/6/12.5 µg (BDP/FF/GB 100/6/12.5 µg per actuation) pMDI, fixed-dose combination of beclometasone dipropionate (BDP) + formoterol fumarate (FF) + glycopyrronium bromide (GB). The study medication was administered at clinical site on Day 1 as single dose by inhalation (4 inhalation in total) using the pMDI device, for a total dose of BDP 400 µg, FF 24 µg, GB 50 µg. The subjects were trained to use the pMDI device with (Aerosol Inhalation Monitor) AIM[™] Vitalograph® at the screening visit and at pre-dose on Day 1.

The subjects were trained also using the pMDI placebo devices at screening and at Day 1.

| Number of subjects in period 1 | Adolescents (12-17 years) | Adults (18-64 years) |
|---------------------------------------|---------------------------|----------------------|
| Started | 40 | 40 |
| Completed | 40 | 40 |

Baseline characteristics

Reporting groups

| | |
|--|---------------------------|
| Reporting group title | Adolescents (12-17 years) |
| Reporting group description: Adolescent asthmatic patients who have received one single-dose (consisting of 4 inhalation) of fixed combination CHF 5993 400/24/50 µg pMDI (400 µg BDP, 24 µg FF, and 50 µg GB). | |
| Reporting group title | Adults (18-64 years) |
| Reporting group description: Adult asthmatic patients who have received one single-dose (consisting of 4 inhalation) of fixed combination CHF 5993 400/24/50 µg pMDI (400 µg BDP, 24 µg FF, and 50 µg GB) | |

| Reporting group values | Adolescents (12-17 years) | Adults (18-64 years) | Total |
|---------------------------------------|---------------------------|----------------------|-------|
| Number of subjects | 40 | 40 | 80 |
| Age categorical Units: Subjects | | | |
| Adolescents (12-17 years) | 40 | 0 | 40 |
| Adults (18-64 years) | 0 | 40 | 40 |
| Age continuous Units: years | | | |
| arithmetic mean | 14.8 | 43.6 | - |
| standard deviation | ± 1.6 | ± 14.7 | |
| Gender categorical Units: Subjects | | | |
| Female | 15 | 26 | 41 |
| Male | 25 | 14 | 39 |
| Race Units: Subjects | | | |
| White | 40 | 40 | 80 |

Subject analysis sets

| | |
|--|------------------------------------|
| Subject analysis set title | Adolescents (12-17 years) - Safety |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: Including all subjects who were enrolled and received at least one dose of study drug. | |
| Subject analysis set title | Adults (18-64 years) - Safety |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: Including all subjects who were enrolled and received at least one dose of study drug. | |
| Subject analysis set title | Adolescents (12-17 years) - PK |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: The PK population included all subjects from the safety set excluding subjects without any valid PK measurement and with major protocol deviation affecting PK evaluations. | |
| Subject analysis set title | Adults (18-64 years)- PK |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: The PK population included all subjects from the safety set excluding subjects without any valid PK | |

measurement and with major protocol deviation affecting PK evaluations.

| | |
|----------------------------|--------------------------------|
| Subject analysis set title | Adolescents (12-17 years) - PD |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

The PD population included all subjects from the safety set excluding subjects without any valid PD measurement and with major protocol deviations affecting PD evaluations.

| | |
|----------------------------|--------------------------|
| Subject analysis set title | Adults (18-64 years)- PD |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

The PD population included all subjects from the safety set excluding subjects without any valid PD measurement and with major protocol deviations affecting PD evaluations.

| Reporting group values | Adolescents (12-17 years) - Safety | Adults (18-64 years) - Safety | Adolescents (12-17 years) - PK |
|---------------------------------------|------------------------------------|-------------------------------|--------------------------------|
| Number of subjects | 40 | 40 | 40 |
| Age categorical Units: Subjects | | | |
| Adolescents (12-17 years) | 40 | 0 | 40 |
| Adults (18-64 years) | 0 | 40 | 0 |
| Age continuous Units: years | | | |
| arithmetic mean | 14.8 | 43.6 | 14.8 |
| standard deviation | ± 1.6 | ± 14.7 | ± 1.6 |
| Gender categorical Units: Subjects | | | |
| Female | 15 | 26 | 15 |
| Male | 25 | 14 | 25 |
| Race Units: Subjects | | | |
| White | 40 | 40 | 40 |

| Reporting group values | Adults (18-64 years)- PK | Adolescents (12-17 years) - PD | Adults (18-64 years)- PD |
|---------------------------------------|--------------------------|--------------------------------|--------------------------|
| Number of subjects | 40 | 38 | 37 |
| Age categorical Units: Subjects | | | |
| Adolescents (12-17 years) | 0 | 38 | 0 |
| Adults (18-64 years) | 40 | 0 | 37 |
| Age continuous Units: years | | | |
| arithmetic mean | 43.6 | 14.7 | 43.4 |
| standard deviation | ± 14.7 | ± 1.6 | ± 14.7 |
| Gender categorical Units: Subjects | | | |
| Female | 26 | 15 | 24 |
| Male | 14 | 23 | 13 |
| Race Units: Subjects | | | |
| White | 40 | 38 | 37 |

End points

End points reporting groups

| | |
|--|------------------------------------|
| Reporting group title | Adolescents (12-17 years) |
| Reporting group description: Adolescent asthmatic patients who have received one single-dose (consisting of 4 inhalation) of fixed combination CHF 5993 400/24/50 µg pMDI (400 µg BDP, 24 µg FF, and 50 µg GB). | |
| Reporting group title | Adults (18-64 years) |
| Reporting group description: Adult asthmatic patients who have received one single-dose (consisting of 4 inhalation) of fixed combination CHF 5993 400/24/50 µg pMDI (400 µg BDP, 24 µg FF, and 50 µg GB) | |
| Subject analysis set title | Adolescents (12-17 years) - Safety |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: Including all subjects who were enrolled and received at least one dose of study drug. | |
| Subject analysis set title | Adults (18-64 years) - Safety |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: Including all subjects who were enrolled and received at least one dose of study drug. | |
| Subject analysis set title | Adolescents (12-17 years) - PK |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: The PK population included all subjects from the safety set excluding subjects without any valid PK measurement and with major protocol deviation affecting PK evaluations. | |
| Subject analysis set title | Adults (18-64 years)- PK |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: The PK population included all subjects from the safety set excluding subjects without any valid PK measurement and with major protocol deviation affecting PK evaluations. | |
| Subject analysis set title | Adolescents (12-17 years) - PD |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: The PD population included all subjects from the safety set excluding subjects without any valid PD measurement and with major protocol deviations affecting PD evaluations. | |
| Subject analysis set title | Adults (18-64 years)- PD |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: The PD population included all subjects from the safety set excluding subjects without any valid PD measurement and with major protocol deviations affecting PD evaluations. | |

Primary: 1_AUC0-t for B17MP (active metabolite of BDP)

| | |
|--|---|
| End point title | 1_AUC0-t for B17MP (active metabolite of BDP) |
| End point description: The AUC0-t for B17MP (the area under the plasma concentration-time curve from 0 to the last quantifiable concentration) was log-transformed and analysed using a linear model including patient group as fixed effects. Data was expressed as arithmetic mean with standard deviation. | |
| End point type | Primary |
| End point timeframe: The AUC0-t for B17MP was studied for up to 10 h after administration of CHF 5993 400/24/50 µg pMDI for B17MP. | |

| End point values | Adolescents (12-17 years) - PK | Adults (18-64 years)- PK | | |
|--------------------------------------|--------------------------------|--------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 40 ^[1] | 38 ^[2] | | |
| Units: h·pg/mL | | | | |
| arithmetic mean (standard deviation) | 3204 (± 909) | 4027 (± 1022) | | |

Notes:

[1] - PK population:
number of patients/number of patients with data:
40/40

[2] - PK population:
number of patients/number of patients with data:
40/38

Statistical analyses

| Statistical analysis title | 1_B17MP AUC0-t ratio of adjusted geometric mean |
|--|---|
| Statistical analysis description: | |
| The ratio of adjusted geometric means (GMR) between patients groups (adolescent vs adult) was calculated with their 90% two sided confidence interval (CIs). Adult and adolescent total systemic exposure (AUC0-t) was assessed as comparable if the upper limit of CIs of the ratios (adolescent vs adult) was lower or equal to 125%. | |
| Comparison groups | Adults (18-64 years)- PK v Adolescents (12-17 years) - PK |
| Number of subjects included in analysis | 78 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.0006 |
| Method | ANOVA |
| Parameter estimate | Ratio (%) |
| Point estimate | 79.28 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 71.19 |
| upper limit | 88.29 |

Primary: 1_AUC0-t for Formoterol (FF)

| End point title | 1_AUC0-t for Formoterol (FF) |
|---|------------------------------|
| End point description: | |
| The AUC0-t for Formoterol (the area under the plasma concentration-time curve from 0 to the last quantifiable concentration) was log-transformed and analysed using a linear model including patient group as fixed effects. Data was expressed as arithmetic mean with standard deviation. | |
| End point type | Primary |
| End point timeframe: | |
| The AUC0-t for Formoterol was studied for up to 10 h after administration of CHF 5993 400/24/50 µg pMDI for Formoterol. | |

| End point values | Adolescents (12-17 years) - PK | Adults (18-64 years)- PK | | |
|--------------------------------------|--------------------------------|--------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 34 ^[3] | 37 ^[4] | | |
| Units: h·pg/mL | | | | |
| arithmetic mean (standard deviation) | 73.8 (± 21.8) | 84.6 (± 26.6) | | |

Notes:

[3] - PK population:
number of patients/number of patients with data:
40/34

[4] - PK population:
number of patients/number of patients with data:
40/37

Statistical analyses

| Statistical analysis title | 1_FF AUC0-t ratio of adjusted geometric mean |
|----------------------------|--|
|----------------------------|--|

Statistical analysis description:

The ratios of adjusted geometric means (GMR) between patients groups (adolescent vs adult) was calculated with their 90% two sided confidence interval (CIs).
Adult and adolescent total systemic exposure (AUC0-t) was assessed as comparable if the upper limit of CIs of the ratios (adolescent vs adult) was lower or equal to 125%.

| | |
|---|---|
| Comparison groups | Adolescents (12-17 years) - PK v Adults (18-64 years)- PK |
| Number of subjects included in analysis | 71 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.1339 |
| Method | ANOVA |
| Parameter estimate | Ratio (%) |
| Point estimate | 88.68 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 77.71 |
| upper limit | 101.2 |

Primary: 1_AUC0-t for Glycopyrronium Bromide (GB)

| | |
|-----------------|--|
| End point title | 1_AUC0-t for Glycopyrronium Bromide (GB) |
|-----------------|--|

End point description:

The AUC0-t for Glycopyrronium Bromide (the area under the plasma concentration-time curve from 0 to the last quantifiable concentration) was log-transformed and analysed using a linear model including patient group as fixed effects. Data was expressed as arithmetic mean with standard deviation.

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

End point timeframe:

The AUC0-t for Glycopyrronium Bromide was studied for up to 10 h after administration of CHF 5993 400/24/50 µg pMDI for Glycopyrronium Bromide.

| End point values | Adolescents (12-17 years) - PK | Adults (18-64 years)- PK | | |
|--------------------------------------|--------------------------------|--------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 40 ^[5] | 38 ^[6] | | |
| Units: h·pg/mL | | | | |
| arithmetic mean (standard deviation) | 74.5 (± 27.5) | 90.1 (± 39.1) | | |

Notes:

[5] - PK population:

number of patients/number of patients with data:

40/40

[6] - PK population:

number of patients/number of patients with data:

40/38

Statistical analyses

| Statistical analysis title | 1_GB AUC0-t ratio of adjusted geometric mean |
|----------------------------|--|
|----------------------------|--|

Statistical analysis description:

The ratios of adjusted geometric means (GMR) between patients groups (adolescent vs adult) was calculated with their 90% two sided confidence interval (CIs).

Adult and adolescent total systemic exposure (AUC0-t) was assessed as comparable if the upper limit of CIs of the ratios (adolescent vs adult) was lower or equal to 125%.

| | |
|---|---|
| Comparison groups | Adults (18-64 years)- PK v Adolescents (12-17 years) - PK |
| Number of subjects included in analysis | 78 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.1035 |
| Method | ANOVA |
| Parameter estimate | Ratio (%) |
| Point estimate | 85.49 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 72.96 |
| upper limit | 100.16 |

Secondary: 2_Cmax for B17MP (active metabolite of BDP)

| | |
|-----------------|---|
| End point title | 2_Cmax for B17MP (active metabolite of BDP) |
|-----------------|---|

End point description:

The Cmax for B17MP (the value of the maximum plasma concentration) was log-transformed and analysed using a linear model including patient group (adolescent or adult) as fixed effects. Data was expressed as arithmetic mean with standard deviation.

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

End point timeframe:

The Cmax for B17MP was studied for up to 10 h after administration of CHF 5993 400/24/50 µg pMDI for B17MP.

| End point values | Adolescents (12-17 years) - PK | Adults (18-64 years)- PK | | |
|--------------------------------------|--------------------------------|--------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 40 ^[7] | 38 ^[8] | | |
| Units: pg/mL | | | | |
| arithmetic mean (standard deviation) | 831 (± 328) | 1046 (± 455) | | |

Notes:

[7] - PK population:
number of patients/number of patients with data:
40/40

[8] - PK population:
number of patients/number of patients with data:
40/38

Statistical analyses

| Statistical analysis title | 2_ B17MP Cmax ratio of adjusted geometric mean |
|----------------------------|--|
|----------------------------|--|

Statistical analysis description:

The ratios of adjusted geometric means (GMR) between patients groups (adolescent vs adult) was calculated with their 90% two sided confidence interval (CIs).
Adult and adolescent maximum plasma concentration (Cmax) was assessed as comparable if the upper limit of CIs of the ratios (adolescent vs adult) was lower or equal to 125%.

| | |
|---|---|
| Comparison groups | Adolescents (12-17 years) - PK v Adults (18-64 years)- PK |
| Number of subjects included in analysis | 78 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.0401 |
| Method | ANOVA |
| Parameter estimate | Ratio (%) |
| Point estimate | 81.07 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 68.58 |
| upper limit | 95.84 |

Secondary: 2_Cmax for Formoterol (FF)

| | |
|-----------------|----------------------------|
| End point title | 2_Cmax for Formoterol (FF) |
|-----------------|----------------------------|

End point description:

The Cmax for Formoterol (the value of the maximum plasma concentration) was log-transformed and analysed using a linear model including patient group (adolescent or adult) as fixed effects. Data was expressed as arithmetic mean with standard deviation.

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

End point timeframe:

The Cmax for Formoterol was studied for up to 10 h after administration of CHF 5993 400/24/50 µg pMDI for Formoterol.

| End point values | Adolescents (12-17 years) - PK | Adults (18-64 years)- PK | | |
|--------------------------------------|--------------------------------|--------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 36 ^[9] | 37 ^[10] | | |
| Units: pg/mL | | | | |
| arithmetic mean (standard deviation) | 20.9 (± 8.27) | 27.2 (± 12.0) | | |

Notes:

[9] - PK population:
number of patients/number of patients with data:
40/36

[10] - PK population:
number of patients/number of patients with data:
40/37

Statistical analyses

| Statistical analysis title | 2_FF Cmax ratio of adjusted geometric mean |
|----------------------------|--|
|----------------------------|--|

Statistical analysis description:

The ratios of adjusted geometric means (GMR) between patients groups (adolescent vs adult) was calculated with their 90% two sided confidence interval (CIs).
Adult and adolescent maximum plasma concentration (Cmax) was assessed as comparable if the upper limit of CIs of the ratios (adolescent vs adult) was lower or equal to 125%.

| | |
|---|---|
| Comparison groups | Adolescents (12-17 years) - PK v Adults (18-64 years)- PK |
| Number of subjects included in analysis | 73 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.032 |
| Method | ANOVA |
| Parameter estimate | Ratio (%) |
| Point estimate | 78.83 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 65.76 |
| upper limit | 94.49 |

Secondary: 2_Cmax for Glycopyrronium Bromide (GB)

| | |
|-----------------|--|
| End point title | 2_Cmax for Glycopyrronium Bromide (GB) |
|-----------------|--|

End point description:

The Cmax for Glycopyrronium Bromide (the value of the maximum plasma concentration) was log-transformed and analysed using a linear model including patient group (adolescent or adult) as fixed effects. Data were expressed as arithmetic mean with standard deviation.

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

End point timeframe:

The Cmax for Glycopyrronium Bromide was studied for up to 10 h after administration of CHF 5993 400/24/50 µg pMDI for Glycopyrronium Bromide.

| End point values | Adolescents (12-17 years) - PK | Adults (18-64 years)- PK | | |
|--------------------------------------|--------------------------------|--------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 40 ^[11] | 38 ^[12] | | |
| Units: pg/mL | | | | |
| arithmetic mean (standard deviation) | 25.6 (± 15.2) | 39.5 (± 31.7) | | |

Notes:

[11] - PK population:
number of patients/number of patients with data:
40/40

[12] - PK population:
number of patients/number of patients with data:
40/38

Statistical analyses

| Statistical analysis title | 2_GB Cmax ratio of adjusted geometric mean |
|----------------------------|--|
|----------------------------|--|

Statistical analysis description:

The ratios of adjusted geometric means (GMR) between patients groups (adolescent vs adult) was calculated with their 90% two sided confidence interval (CIs).

Adult and adolescent maximum plasma concentration (Cmax) was assessed as comparable if the upper limit of CIs of the ratios (adolescent vs adult) was lower or equal to 125%.

| | |
|---|---|
| Comparison groups | Adolescents (12-17 years) - PK v Adults (18-64 years)- PK |
| Number of subjects included in analysis | 78 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.0583 |
| Method | ANOVA |
| Parameter estimate | Ratio (%) |
| Point estimate | 76 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 59.92 |
| upper limit | 96.39 |

Secondary: 3_Glucose Serum Pharmacodynamic Parameter (Cmax)

| | |
|-----------------|--|
| End point title | 3_Glucose Serum Pharmacodynamic Parameter (Cmax) |
|-----------------|--|

End point description:

The Cmax (value of maximum serum concentration of Glucose) data was expressed as arithmetic mean with standard deviation.

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

End point timeframe:

The Cmax of Glucose was studied in serum up to 4 h after administration of CHF 5993 400/24/50 µg pMDI.

| End point values | Adolescents (12-17 years) - PD | Adults (18-64 years)- PD | | |
|--------------------------------------|--------------------------------|--------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 38 ^[13] | 37 ^[14] | | |
| Units: millimole(s)/litre | | | | |
| arithmetic mean (standard deviation) | 7.09 (± 1.49) | 7.78 (± 1.60) | | |

Notes:

[13] - PD population:
number of patients/number of patients with data:
38/38

[14] - PD population:
number of patients/number of patients with data:
37/37

Statistical analyses

No statistical analyses for this end point

Secondary: 3_Glucose Serum Pharmacodynamic Parameter (t max)

| | |
|-----------------|---|
| End point title | 3_Glucose Serum Pharmacodynamic Parameter (t max) |
|-----------------|---|

End point description:

The tmax (time of the maximum serum concentration of Glucose) data was expressed with median (minimum-maximum).

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

End point timeframe:

The tmax of Glucose was studied in serum up to 4 h after administration of CHF 5993 400/24/50 µg pMDI.

| End point values | Adolescents (12-17 years) - PD | Adults (18-64 years)- PD | | |
|-------------------------------|--------------------------------|--------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 38 ^[15] | 37 ^[16] | | |
| Units: hour | | | | |
| median (full range (min-max)) | 4.0 (0.0 to 4.08) | 4.02 (2.02 to 4.05) | | |

Notes:

[15] - PD population:
number of patients/number of patients with data:
38/38

[16] - PD population:
number of patients/number of patients with data:
37/37

Statistical analyses

No statistical analyses for this end point

Secondary: 3_Glucose Serum Pharmacodynamic Parameter (AUC0-2h)

| | |
|--|---|
| End point title | 3_Glucose Serum Pharmacodynamic Parameter (AUC0-2h) |
| End point description: The AUC0-2h (the area under the serum concentration versus time curve observed from time 0 up to 2h time point) data was expressed as arithmetic mean with standard deviation. | |
| End point type | Secondary |
| End point timeframe: The AUC0-2h of Glucose was studied in serum up to 4 h after administration of CHF 5993 400/24/50 µg pMDI. | |

| End point values | Adolescents (12-17 years) - PD | Adults (18-64 years)- PD | | |
|--------------------------------------|--------------------------------|--------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 38 ^[17] | 37 ^[18] | | |
| Units: h·mmol/L | | | | |
| arithmetic mean (standard deviation) | 10.4 (± 0.923) | 11.3 (± 1.20) | | |

Notes:

[17] - PD population:
number of patients/number of patients with data:
38/38

[18] - PD population:
number of patients/number of patients with data:
37/37

Statistical analyses

No statistical analyses for this end point

Secondary: 3_Potassium Serum Pharmacodynamic Parameter (Cmin)

| | |
|--|--|
| End point title | 3_Potassium Serum Pharmacodynamic Parameter (Cmin) |
| End point description: The Cmin (value of minum Potassium serum level) data was expressed as arithmetic mean with standard deviation. | |
| End point type | Secondary |
| End point timeframe: The Cmin of Potassium was studied in serum up to 4 h after administration of CHF 5993 400/24/50 µg pMDI. | |

| End point values | Adolescents (12-17 years) - PD | Adults (18-64 years)- PD | | |
|--------------------------------------|--------------------------------|--------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 35 ^[19] | 36 ^[20] | | |
| Units: millimole(s)/litre | | | | |
| arithmetic mean (standard deviation) | 4.17 (± 0.370) | 3.91 (± 0.306) | | |

Notes:

[19] - PD population:
number of patients/number of patients with data:
38/35

[20] - PD population:

Statistical analyses

No statistical analyses for this end point

Secondary: 3_Potassium Serum Pharmacodynamic Parameter (t min)

| | |
|-----------------|---|
| End point title | 3_Potassium Serum Pharmacodynamic Parameter (t min) |
|-----------------|---|

End point description:

The tmin (time of minimum Potassium serum level) data was expressed as median (minimum-maximum).

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

End point timeframe:

The tmin of Potassium was studied in serum up to 4 h after administration of CHF 5993 400/24/50 µg pMDI.

| End point values | Adolescents (12-17 years) - PD | Adults (18-64 years)- PD | | |
|-------------------------------|--------------------------------|--------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 35 ^[21] | 36 ^[22] | | |
| Units: hour | | | | |
| median (full range (min-max)) | 2.0 (0.00 to 4.00) | 2.02 (0.00 to 4.05) | | |

Notes:

[21] - PD population:

number of patients/number of patients with data:
38/35

[22] - PD population:

number of patients/number of patients with data:
37/36

Statistical analyses

No statistical analyses for this end point

Secondary: 3_Potassium Serum Pharmacodynamic Parameter (AUC0-2h)

| | |
|-----------------|---|
| End point title | 3_Potassium Serum Pharmacodynamic Parameter (AUC0-2h) |
|-----------------|---|

End point description:

The AUC0-2h (the area under the serum concentration versus time curve observed from time 0 up to 2h time point) data was expressed as arithmetic mean with standard deviation.

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

End point timeframe:

The AUC0-2 of Potassium was studied in serum up to 4 h after administration of CHF 5993 400/24/50 µg pMDI.

| End point values | Adolescents (12-17 years) - PD | Adults (18-64 years)- PD | | |
|--------------------------------------|--------------------------------|--------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 29 ^[23] | 36 ^[24] | | |
| Units: h·mmol/L | | | | |
| arithmetic mean (standard deviation) | 8.83 (± 0.584) | 8.34 (± 0.629) | | |

Notes:

[23] - PD population:

number of patients/number of patients with data:

38/29

[24] - PD population:

number of patients/number of patients with data:

37/36

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs were recorded from the time of the Informed Consent signature until the patient's study participation ends.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 23.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------------------------|
| Reporting group title | Adolescents (12-17 years) |
|-----------------------|---------------------------|

Reporting group description:

40 adolescent patients treated with fixed combination of CHF 5993 400/24/50 µg pMDI

| | |
|-----------------------|----------------------|
| Reporting group title | Adults (18-64 years) |
|-----------------------|----------------------|

Reporting group description:

40 adult patients treated with fixed combination of CHF 5993 400/24/50 µg pMDI

| Serious adverse events | Adolescents (12-17 years) | Adults (18-64 years) | |
|---|---------------------------|----------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | 0 / 40 (0.00%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |

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

| Non-serious adverse events | Adolescents (12-17 years) | Adults (18-64 years) | |
|---|---------------------------|----------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | 3 / 40 (7.50%) | |
| Nervous system disorders | | | |
| Dysgeusia | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | 1 / 40 (2.50%) | |
| occurrences (all) | 0 | 1 | |
| General disorders and administration site conditions | | | |
| Non-cardiac Chest Pain | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | 1 / 40 (2.50%) | |
| occurrences (all) | 0 | 1 | |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | |
|--|---------------------|---------------------|--|
| Cough subjects affected / exposed occurrences (all) | 0 / 40 (0.00%) 0 | 1 / 40 (2.50%) 1 | |
| Psychiatric disorders Anxiety subjects affected / exposed occurrences (all) | 0 / 40 (0.00%) 0 | 1 / 40 (2.50%) 1 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|---|
| 27 January 2020 | The first revised CTP (version 2.0, dated 7 January 2020) was issued following feedback from the Competent Authority. The following changes were made: to document the change in Sponsor Medical Expert, to include a lower limit of body weight in the inclusion criteria, and to change the serum pregnancy test at screening to a urine pregnancy test. In addition, the timing of the screening and follow-up visits was updated, the allowed time deviation from theoretical post-dose times was added for PD assessments between 10 and 24 h post-dose, and the volume of blood samples for laboratory evaluations was reduced. |
| 10 June 2020 | The second revised CTP (version 3.0, dated 24 April 2020) submitted on 30 April 2020 (silent/implicit approval from 10 June 2020) has been modified to: adjust the Hb value in the exclusion criteria to be in line with adolescent values, define time zero more clearly, better explain the ICF procedure, clarify when Holter recording should start, reduce the fasting period from 4 to 2 h post-dose and adjust the AUC of potassium and glucose accordingly, include reference to the Investigator's Brochure for CHF 5993 in the definition of predictability of AEs, and differentiate the required volume of blood samples for laboratory evaluations between adolescents and adults. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported