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 Trasparency, Chiesi Farmaceutici S.p.A, clinicaltrials_info@chiesi.com
Scientific contact	Clinical Trial Trasparency, 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)	EMEA-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 (AUC0-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 obtain 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 trainded 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 subjectss were trainded 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 adolecent 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 adolecent 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 adolecent 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 ofthe 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:
numberof 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 adolecent 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 adolecent 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 ofthe 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 adolecent 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:

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 (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 partecipation 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