EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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EMA/38576/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Trimbow

beclometasone / formoterol / glycopyrronium bromide

Procedure no: EMEA/H/C/004257/P46/003

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Introduction

On 29 July 2021, the MAH submitted a completed paediatric study for CHF 5993 100/6/12.5 mcg pressurised inhalation solution (EMEA/H/C/004257, tradename Trimbow), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are also submitted as part of the post-authorisation measures. A short critical expert has also been provided.

2. Scientific discussion

2.1. Information on the development program

CHF 5993 pressurised metered dose inhaler (pMDI) is a fixed dose combination (FDC) of the inhaled corticosteroid (ICS) beclometasone dipropionate (BDP), the long-acting β2-agonist (LABA) formoterol fumarate (FF) and the long-acting muscarinic antagonist (LAMA) glycopyrronium bromide (GB).

The medicinal product was first authorised by the European Commission (EC) in July 2017 for the maintenance treatment of adult patients with moderate to severe chronic obstructive pulmonary disease (COPD) whose symptoms are not adequately controlled by a combination of ICS / LABA. In January 2019, the indication was broadened via a type II variation to also include patients not adequately controlled by a combination of ICS / LAMA.

In January 2021, CHF 5993 pMDI 100/6/12.5 was also authorised by the EC for the maintenance treatment of asthma patients not adequately controlled by a combination of a LABA and medium dose ICS and having experienced one or more asthma exacerbations in the previous year.

The authorised dose regimen for CHF 5993 pMDI 100/6/12.5 in adult patients with COPD and asthma is **2 puffs twice daily** (bid).

The development of CHF 5993 pMDI in adolescents (12 to 17 years of age) plans to use the commercially available formulation and strength of CHF 5993 approved in adult patients with COPD and asthma (dose strength 100/6/12.5 mcg, referred to as medium strength).

A Paediatric Investigation Plan (PIP) was initially agreed with the PDCO in May 2019 and modified afterwards three times, in November 2019, August 2020 and March 2021, respectively. Due to the global Coronavirus pandemic outbreak, execution of the agreed PIP and studies was delayed.

The clinical pharmacology / PK safety study in scope of this application (study **CLI-05993CB1-01**) is the first out of two clinical studies (to be) conducted by the applicant as part of the agreed paediatric investigational plan (PIP, most recent version P/0094/2021 issued on 17MAR2021). The main objective of the study was to quantify total systemic exposure to CHF 5993 (as a surrogate of safety) in an **adolescent population** as compared with adults after a single dose consisting of a total of four consecutive inhalations (total nominal dose: 400 mcg BDP, 24 mcg FF, and 50 mcg GB).

Based on the results of this study, an active controlled safety and efficacy study in adolescents is planned to be conducted next by the applicant (study **CLI-05993CB1-02**).

2.2. Information on the pharmaceutical formulation used in the study

In the PK study **CLI-05993CB1-01**, the commercially available pMDI formulation and strength of CHF 5993 approved adult patients with COPD and asthma (dose strength 100/6/12.5 mcg, referred to as medium strength) was used.

2.3. Clinical aspects

2.3.1. Introduction

In the framework of this submission, the MAH submitted the final clinical study report (CSR) for:

- study **CLI-05993CB1-01**

  Study title: *A single-dose, uncontrolled, open label, non-randomised, clinical pharmacology study of CHF 5993 100/6/12.5 µg pMDI (fixed combination of beclometasone dipropionate plus formoterol fumarate plus glycopyrronium bromide) in asthmatic adolescent patients and adult patients*

  LPLV of the study was on 04FEB2021 and the report issued on 23JUL2021. The CSR is thus submitted within six (6) months from study completion as required by applicable regulation.

2.3.2. Clinical study

Clinical study CLI-05993CB1-01

Description

This was a single-dose, uncontrolled, open-label, non-randomised study to characterise the pharmaco-kinetics, safety and tolerability of CHF 5993 100/6/12.5 mcg pMDI in asthmatic adolescent patients as compared to adults.

Methods

Objective(s)

Primary objectives

-to evaluate the total systemic exposure to the active ingredients of CHF 5993 (B17MP, formoterol and GB) as measured by the area under the plasma concentration-time curve (AUC) from 0 to the last quantifiable concentration (AUC0-t) after inhalation of CHF 5993 pMDI in adolescent asthmatic patients in comparison to adult asthmatic patients;

-to evaluate the pharmacokinetic (PK) profile of BDP and additional PK parameters of B17MP, formoterol, and GB;

-to evaluate the systemic effects in terms of heart rate (HR), serum potassium and glucose levels and the general safety and tolerability profile of CHF 5993 pMDI in adolescent asthmatics as compared with adult asthma patients.

Study design

An overview on the study design is provided in Figure 1. Patients who met the eligibility criteria upon the screening were enrolled into the study. Patients presented to the clinical unit on the morning of day D1 with

no prior in-house stay. Once the eligibility was re-confirmed and the pre-dose assessments completed, study participants administered a single dose of CHF 5993 and remained in-house until the 10-hour post-dose assessments had been completed. On day D2 of the study, study participants came back to the clinical unit for further post-dose assessments. Fourteen (14) to sixteen (16) days after IMP administration, an end-of-study visit took place.

Figure 1: Study design and visits

GCP aspects

The applicant confirms that the study was conducted in compliance with ICH-GCP and other applicable international regulations and guidance. According to the documentation submitted by the applicant, maintenance audits of the service providers entrusted with on-site monitoring, PK/PD-analyses, data management biostatistics, medical writing and cardiac safety analyses were performed.

Laboratory analyses were carried out according to GCP and the applicable principles of Good Laboratory Practice (GLP) regulations of the Organisation for Economic Co-operation and Development (OECD.

No major deviations from the CTP were reported by study sponsor.

Study population /Sample size

The study population included male and female adolescent and adult patients with a diagnosis of asthma for at least 6 months prior to the screening visit. Participants had to be on regular treatment with medium doses of ICS alone or in fixed combination with long-acting β2-agonist (LABA) and using short-acting β2-agonist (SABA) as reliever. In line with the GINA 2019 guideline, asthma disease had to be controlled in order to be able to wash out BDP and other corticosteroids two days before the IMP was administered. In order to be eligible, participants had to have a forced expiratory volume in one second (FEV1) of >70% of predicted values after withholding treatment for a minimum of 6h prior to screening or 24h in case of LABA. Further criteria were consistent with accepted standards for this type of clinical research involving an asthma population.

The required sample size was calculated to be N=74 evaluable patients (assumed standard deviation of 0.38 on a log-scale; 80% power to rule out that the ratio in total systemic exposure between adolescents and adults is greater than 125%; two-sided 90% confidence interval). Considering a rate of non-evaluable participants of approx. 7%, a total of 80 patients (40 adolescents and 40 adults) were planned to be enrolled.

All 40 eligible subjects (100%) enrolled in the two age groups were treated with the IMP and also completed the PK part of the study. The PD analysis set consisted of N=75 patients (N=38 adolescents and N=37 adults).

Treatments

Prior to IMP administration, all participants were instructed and received documented training to correctly use the pMDI device using an aerosol inhalation monitor (AIM™ Vitalograph).

On day D1, all participants administered one single dose of CHF 5993 from one inhaler, consisting of four consecutive inhalations of CHF 5993 100/6/12.5 µg pMDI (total nominal dose: 400 mcg BDP, 24 mcg FF and 50 mcg GB).

Patients were instructed to hold their breath for 10 seconds following each inhalation and to wait approximately 30 seconds before administering the next inhalation. This resulted in an interval of 40 seconds between consecutive inhalations. Time zero was defined as the time when the first inhalation was initiated and thus, all post-dose measurement times of PK and PD parameters refer to this time point.

Any issues observed by the investigator(s) or their designee(s) during the inhalation manoeuvres were recorded in the eCRF.

Outcomes/endpoints

A total of nine blood samples collected up to 10 hours post-dose (pre, 5', 15', 30', 1h, 2h, 4h, 8h and 10h post-dose) to quantify the concentrations of BDP, B17-MP formoterol and GB (*pharmacokinetic part*).

- primary variables
  AUC_{0-t} of B17MP, formoterol and GB;
- secondary variables
  C_{max}, t_{max}, $AUC_{0-0.5h}$, $AUC_{0-\infty}$ and $t_{½}$ of B17MP, formoterol and GB;
  AUC_{0-t}, C_{max} and t_{max} of BDP.

The following *pharmacodynamic parameters* were recorded:

- serum potassium: AUC_{0-2h}, AUC_{0-t} , C_{min}, t_{min};
- serum glucose: AUC_{0-2h}, AUC_{0-t} , C_{max}, t_{max};
- heart rate (HR): average pre-dose, 0-4h, 0-12h and 0-24h;
- 12-lead ECG parameters extracted from Holter: HR, PR, QRS and QTcF;
- blood pressure: systolic and diastolic blood pressure.

Safety variables:

- number of AEs recorded throughout the duration of the study;
- number and percentage of patients who experienced at least one AE;
- clinical laboratory test results (chemistry, hematology and urinalysis).

Statistical Methods

The statistical analysis plan (SAP) was finalised on 14 April 2021 and thus prior to database lock (06 May 2021). Calculations of PK and PD (potassium and glucose) parameters was performed using WinNonlin Phoenix 8.0. All statistical calculations were performed using SAS software version 9.4.

Pharmacokinetic analyses: The PK analysis set was used for all PK analyses; no patients were excluded from this analysis set. PK analyses were based on actual times. PK parameters were calculated, where data permitted, by standard non-compartmental methods. Cmax and tmax were obtained directly from the experimental data without interpolation.

AUC_{0-t} of B17MP, formoterol and GB was log-transformed and analysed using a linear model including patient group (adolescent or adult) as fixed effects. The ratios of adjusted geo means between patient groups (adolescent vs. adult) were calculated with their 90% two-sided CIs. Adolescent and adult total systemic exposure was assessed as comparable if the upper limit of CIs of the ratios (adolescent vs. adult) was lower or equal to 125. Forest plots of the GMR including the respective 90% CIs were to be

graphically presented for the inferential statistical comparison (adolescents vs adults) of AUC0-t, AUC0-0.5h and Cmax of B17MP, formoterol and GB, respectively.

Pharmacodynamic analyses:

Serum potassium and serum glucose concentrations / time curves were descriptively analysed and graphically displayed (by age group) in linear/linear scale.

Parameters of BP and ECG parameters extracted from Holter (HR, PR, QRS, and QTcF; HR0-4h, HR0-12h, and HR0-24h) were also descriptively analysed by age category. Actual values and changes from baseline (incl. corresponding 95% CI) were tabulated separately. For QTcF, the number and percentage of patients with abnormal actual values and/or abnormal changes from baseline were calculated.

Results

Recruitment/ Number analysed

The study was conducted at 2 clinical sites in Poland from 27FEB2020 (first patient first visit, FPFV) until 04FEB2021 (last patient last visit, LPLV).

Due to the COVID-19 pandemic, the enrolment was stopped and/or trial conduct suspended repeatedly. Risk assessment documents were released by the sites to ensure that relevant precautions were taken to guarantee the safety of study participants, their relatives and of site staff. On-site monitoring visits were suspended during the first phase of the pandemic outbreak until June 2020 but are reported to have resumed at times in a limited form from July 2020 onwards. According to the applicant, restrictions and precautions slowed down the Source Data Verification (SDV) activities but did not prevent a full check of the study data. To achieve this objective, remote monitoring was allowed.

In total, 41 adolescent patients and 41 adult patients were screened of whom N=1 (2.4%) adolescent patient and N=1 (2.4%) adult patient were classified to be screening failures. Thus, N=40 adolescent patients and N=40 adult patients were enrolled, received the dose of IMP as defined in the CTP and completed the study. The three analysis sets of study CLI-05993CB1-01 are presented in Table 1.

Table 1: Analysis sets of study CLI-05993CB1-01

	Adolescents N=40	Adults N=40
Safety Set	40 (100.0)	40 (100.0)
PK Analysis Set	40 (100.0)	40 (100.0)
PD Analysis Set	38 (95.0)	37 (92.5)

N=Number of patients

The PK analysis set was defined as all patients of the safety set excluding those without any valid PK measurement and with major protocol deviations affecting PK evaluations. In reality, the PK population consisted of less than N=40 participants for the three analytes in both age groups because a number of instances were observed, leading to the exclusion of data from analyses or rendering data unreliable (in the assessment of the study sponsor). The detailed reasons on which the sponsor's decision was based, are not clearly presented and therefore difficult to understand, at least in part. The document relevant to probably understand in a more straightforward way the decisions taken by the study sponsor in relation with protocol deviations and the exclusion of participants and/or individual results from certain analyses was not submitted (so-called Data Review Report, DRR).

In the following, a brief overview on the most important issues is provided in the following (**Table 2**, **Table 3**).

Quantifiable pre-dose concentrations (>5% of individual Cmax) were reported in this PK study for the following analytes and subjects. Respective data were excluded not only from the statistical PK analyses for the analyte concerned, but also all PD assessments.

Table 2: Subjects with pre-dose plasma concentration (per analyte; PK population)

Analyte	age group	pre-dose conc. (pg/mL)	% of indiv. Cmax
B17-MP	adult	42	5.3%
Formoterol	adolescent	1.55 4.39	8.9% 13.0%
	adult	3.54 1.44 1.15	15.7% 10.1% 5.7%
GB	adult	12.1 16.5	28.9% 62.7%

There were also multiple instances of missing plasma concentrations, rendering the estimation of PK parameters impossible or unreliable (in the assessment of the study sponsor).

Table 3: Subjects with missing plasma concentrations with impact on PK analyses (per analyte; PK population)

Analyte	age group	missing sample(s)	decision
B17-MP	adult	30'	*subject excluded from all analyses*
Formoterol	adolescent	all, but4h	*No estimation of PK parameters possible*
		1h, 4h, 10h	*AUC0-0.5h, tmax, and Cmax included, AUC0-t, AUC0-∞, and t1/2 excluded*
		10h	*AUC0-0.5h, tmax, Cmax and t1/2 included, AUC0-t and AUC0-∞ excluded*
GB	na	none reported	

Several blood samples were taken outside the permitted time windows; respective results were excluded from the descriptive analyses of plasma concentrations but included in the PK parameter estimation.

Baseline data

The gender distribution between the age groups was uneven: whereas 62.5% of the adolescents population were male, this percentage was only 35.0% in the adult age group. The mean (min-max) age was 14.8 (12-17) years for adolescents and 43.6 (19-64) years for adults. Their mean (SD) BMI was 22.3 (3.7) kg/m2 and 25.35 (3.0) kg/m2, respectively. All patients in both age categories were white and – as per inclusion criteria - non-smokers.

At study entry, the vast majority of patients in the adolescent and adult group was on a fixed combination ICS / LABA treatment regimen (77.5% and 92.5%, respectively). Mean (SD) screening FEV1 value was 3.512 (0.772) L for adolescent patients versus 2.636 (0.813) L for adult patients, corresponding to 101.39% (range: 74-144) vs 83.47% (range:71-112) of the predicted normal value. A small percentage of patients in both groups reported to have experienced at least one asthma exacerbation in the previous 12 months (10.0% vs 12.5%).

Efficacy results

- ***Pharmacokinetics***

Comparative pharmacokinetics in adolescents and adult asthma patients after administration of a single, supratherapeutic dose of CHF 5993 (twice the approved adult clinical dose; nominal dose BDP/FF/GB of 400/24/50 mcg) were studied up to 10h post-dose for the metabolite B17-MP, formoterol and GB. Due to the inadequate sampling schedule for the parent compound BDP, these results have only limited relevance to the research question of this study.

The total systemic bioavailability (AUC0-t) as assessed in this study is reflecting the pulmonary disposition as well as the gastrointestinal absorption of swallowed active ingredients, and thus is a surrogate of the orally inhaled medicinal product's safety.

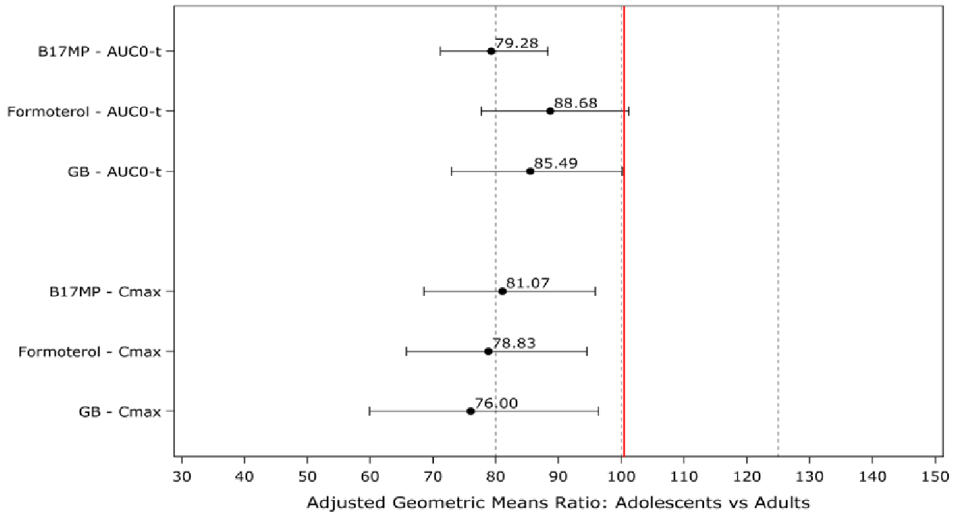
In adolescents, AUC0-t was (markedly) lower for all three primary analytes (B17-MP, formoterol, GB) when compared with adult plasma levels. Similarly, peak plasma concentration (Cmax) of all three analytes were (markedly) lower in adolescents. Overall, the elimination half-live t1/2 was shorter for the adolescents as compared to the adult levels (Table 4, Figure 2).

The median time to peak plasma concentrations (Tmax) was comparable between the age groups, though it needs to be mentioned that the early sampling frequency of blood samples (5', 15' and 30' post-dose) was not adapted to the rapid pulmonary disposition of FF and GB. This is even more true for the parent compound BDP where plasma levels were only quantifiable upon three measurement times, i.e. 5', 15' and 30' post-dose. Results for these three measurement times – with all necessary reservations – may point towards a lower pulmonary disposition in adolescent patients as compared with adults (point estimator of AUC0-0.5h 3.4 (90%CI [24.4-51.2]).

Table 4: Pharmacokinetic conclusions for the primary analytes

Analyte	AUC0-t (PE; [90%CI])	Cmax (90%CI)	Tmax (minutes)	$t^1/_2$ (90%CI)
B17-MP	↙ (79; [71-88])	↙ (81; [66-96])	± (30')	± (88; [81-96])
Formoterol	↙ (87; [78-101])	↙ (79; [66-95])	± (5')	↙ (85; [77-94])
GB	↙ (85; [73-100])	↙ (76; [60-96])	± (5')	↙ (90; [79-102])

Figure 2: AUC0-t and Cmax for each of the three main analytes in adolescents versus adults – Forest plot (PK analysis set)



Thus, the primary objective of the study to rule out a higher systemic plasma exposure (in terms of AUC0-t) to B17MP, formoterol and GB, if the medium dose strength of CHF5993 approved in an adult asthma population is administered in adolescents, was achieved. The upper limit of the respective 90%CI remained below the threshold of 125% for all three analytes.

More detailed results are displayed for each of the three analytes in turn in Figure 3 to Figure 5 as well as in Table 5 to Table 11. It is noted that – based on source data - the PK parameter *AUC0-0.05h* included the tables of the CSR most likely is a typo and should read truncated *AUC0-0.5h*.

- ***Pharmacokinetics – B17MP***

Figure 3: B17MP – mean plasma concentration vs time profile (PK analysis set)

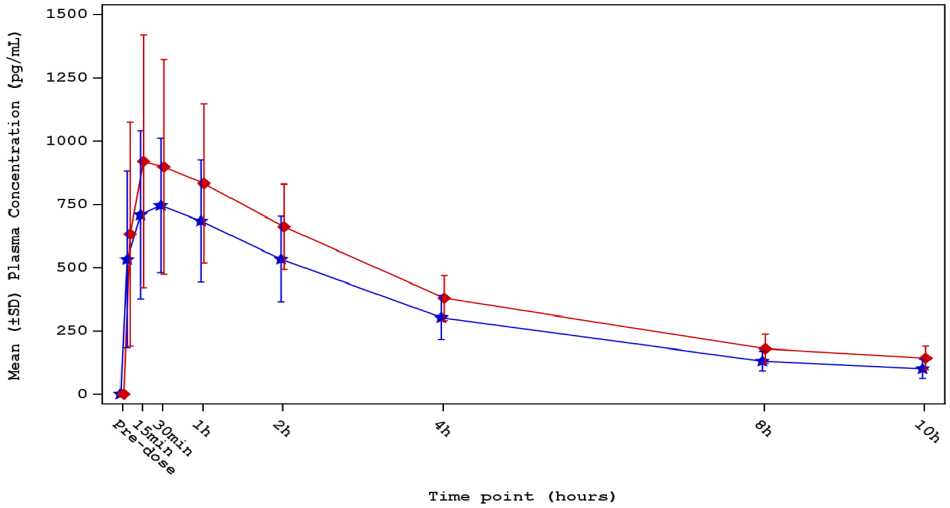


Table 5: B17MP - summary of plasma PK parameters (PK analysis set)

PK Parameter (unit)	Adolescent CHF 5993 400/24/50 µg pMDI N=40	Adult CHF 5993 400/24/50 µg pMDI N=40
C_{max} (pg/mL)	831 (328)	1046 (455) [n=38]
t_{max} (h)	0.50 (0.08; 2.00)	0.50 (0.08; 2.02) [n=38]
$AUC_{0\text{-}0.05h}$ (h.pg/mL)	307 (134)	381 (205) [n=38]
$AUC_{0\text{-}t}$ (h.pg/mL)	3204 (909)	4027 (1022) [n=38]
$AUC_{0\text{-}\infty}$ (h.pg/mL)	3660 (1058) [n=36]	4764 (1282) [n=24]
$t_{1/2}$ (h)	3.47 (0.633) [n=39]	4.00 (1.11) [n=38]

N=number of patients; n=number of patients with data
Values are arithmetic mean (SD), except for t_{max}: median (min; max).

Table 6: B17MP – inferential statistical analysis results (PK analysis set)

PK Parameter (unit)	Adolescent CHF 5993 400/24/50 µg pMDI vs. Adult CHF 5993 400/24/50 µg pMDI	
	n	PE (90% CI)[a]
C_{max} (pg/mL)	40/38	81.07 (68.58; 95.84)
t_{max} (h)	40/38	0.00 (-0.02; 0.23)
$AUC_{0\text{-}0.05h}$ (h.pg/mL)	40/38	86.74 (69.88; 107.67)
$AUC_{0\text{-}t}$ (h.pg/mL)	40/38	79.28 (71.19; 88.29)
$AUC_{0\text{-}\infty}$ (h.pg/mL)	36/24	76.65 (67.40; 87.16)
$t_{1/2}$ (h)	39/38	88.47 (81.22; 96.36)

n=number of patients with data (adolescent/adult)
[a] Point estimate and 90% CI of the ratios of adjusted geometric means of log-transformed parameters from the linear model, except for t_{max}: the Hodges-Lehmann non-parametric estimate of location shifts based on untransformed data is provided with its 90% CI.

- ***Pharmacokinetics – Formoterol***

Figure 4: Formoterol – mean plasma concentration vs time profile (PK analysis set)

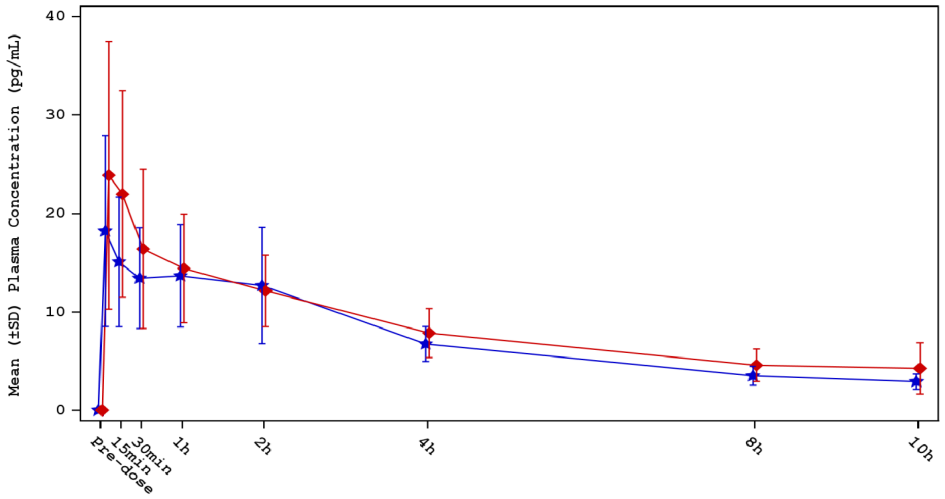


Table 7: Formoterol - summary of plasma PK parameters (PK analysis set)

PK Parameter (unit)	Adolescent CHF 5993 400/24/50 µg pMDI N=40	Adult CHF 5993 400/24/50 µg pMDI N=40
C_{max} (pg/mL)	20.9 (8.27) [n=36]	27.2 (12.0) [n=37]
t_{max} (h)	0.08 (0.08; 4.00) [n=36]	0.08 (0.08; 2.02) [n=37]
$AUC_{0\text{-}0.05h}$ (h.pg/mL)	7.12 (2.95) [n=36]	9.75 (4.59) [n=37]
$AUC_{0\text{-}t}$ (h.pg/mL)	73.8 (21.8) [n=34]	84.6 (26.6) [n=37]
$AUC_{0\text{-}\infty}$ (h.pg/mL)	93.0 (26.5) [n=17]	92.8 (36.5) [n=9]
$t_{1/2}$ (h)	4.46 (1.20) [n=32]	5.25 (1.43) [n=33]

N=number of patients; n=number of patients with data
Values are arithmetic mean (SD), except for t_{max}: median (min; max).

Table 8: Formoterol – inferential statistical analysis results (PK analysis set)

PK Parameter (unit)	Adolescent CHF 5993 400/24/50 µg pMDI vs. Adult CHF 5993 400/24/50 µg pMDI	
	n	PE (90% CI)[a]
C_{max} (pg/mL)	36/37	78.83 (65.76; 94.49)
t_{max} (h)	36/37	0.00 (0.00; 0.00)
$AUC_{0\text{-}0.05h}$ (h.pg/mL)	36/37	77.87 (62.38; 97.20)
$AUC_{0\text{-}t}$ (h.pg/mL)	34/37	88.68 (77.71; 101.20)
$AUC_{0\text{-}\infty}$ (h.pg/mL)	17/9	103.95 (82.52; 130.94)
$t_{1/2}$ (h)	32/33	85.27 (77.04; 94.38)

n=number of patients with data (adolescent/adult)
[a] Point estimate and 90% CI of the ratios of adjusted geometric means of log-transformed parameters from the linear model, except for t_{max}: the Hodges-Lehmann non-parametric estimate of location shifts based on untransformed data is provided with its 90% CI.

- ***Pharmacokinetics – Glycopyrronium bromide (GB)***

Figure 5: GB – mean plasma concentration vs time profile (PK analysis set)

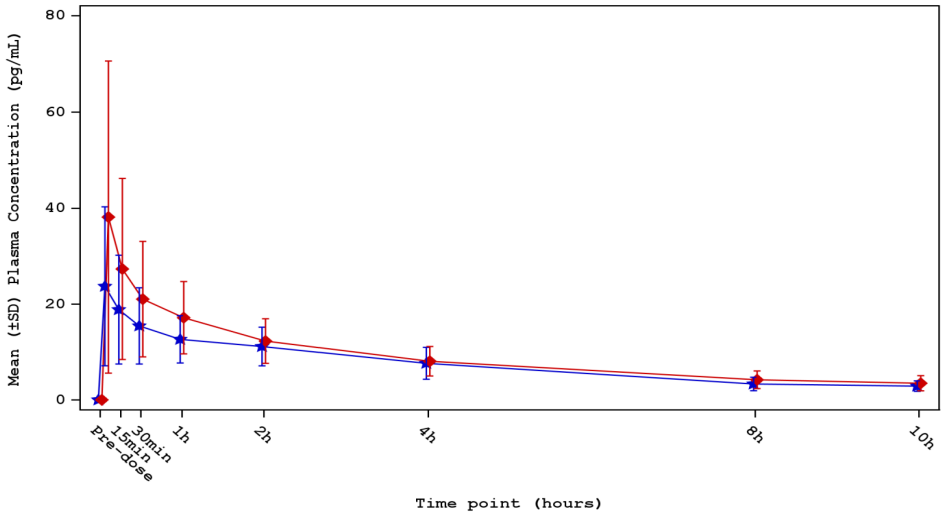


Table 9: GB - summary of plasma PK parameters (PK analysis set)

PK Parameter (unit)	Adolescent CHF 5993 400/24/50 µg pMDI N=40	Adult CHF 5993 400/24/50 µg pMDI N=40
C_{max} (pg/mL)	25.6 (15.2)	39.5 (31.7) [n=38]
t_{max} (h)	0.08 (0.08; 2.00)	0.08 (0.08; 2.02) [n=38]
$AUC_{0\text{-}0.05h}$ (h.pg/mL)	8.81 (5.21)	13.3 (9.60) [n=38]
$AUC_{0\text{-}t}$ (h.pg/mL)	74.5 (27.5)	90.1 (39.1) [n=38]
$AUC_{0\text{-}\infty}$ (h.pg/mL)	91.7 (31.4) [n=27]	102 (47.7) [n=20]
$t_{1/2}$ (h)	4.20 (1.66) [n=38]	4.75 (1.91) [n=37]

N=number of patients; n=number of patients with data
Values are arithmetic mean (SD), except for t_{max}: median (min; max).

Table 10: GB – inferential statistical analysis results (PK analysis set)

PK Parameter (unit)	Adolescent CHF 5993 400/24/50 µg pMDI vs. Adult CHF 5993 400/24/50 µg pMDI	
	n	PE (90% CI)[a]
C_{max} (pg/mL)	40/38	76.00 (59.92; 96.39)
t_{max} (h)	40/38	0.00 (0.00; 0.00)
$AUC_{0\text{-}0.05h}$ (h.pg/mL)	40/38	74.25 (58.44; 94.35)
$AUC_{0\text{-}t}$ (h.pg/mL)	40/38	85.49 (72.96; 100.16)
$AUC_{0\text{-}\infty}$ (h.pg/mL)	27/20	93.15 (77.88; 111.42)
$t_{1/2}$ (h)	38/37	90.04 (79.31; 102.23)

n=number of patients with data (adolescent/adult)
[a] Point estimate and 90% CI of the ratios of adjusted geometric means of log-transformed parameters from the linear model, except for t_{max}: the Hodges-Lehmann non-parametric estimate of location shifts based on untransformed data is provided with its 90% CI.

- ***Pharmacokinetics – BDP***

Table 11: BDP – inferential statistical analysis results (PK analysis set)

PK Parameter (unit)	Adolescent CHF 5993 400/24/50 µg pMDI vs. Adult CHF 5993 400/24/50 µg pMDI	
	n	PE (90% CI)[a]
C_{max} (pg/mL)	40	31.56 (22.32; 44.63)
t_{max} (h)	40	0.00 (0.00; 0.00)
AUC_{0-t} (h.pg/mL)	40	35.35 (24.42; 51.17)

n=number of patients with data

[a] Point estimate and 90% CI of the ratios of adjusted geometric means of log-transformed parameters from the linear model, except for t_{max}: the Hodges-Lehmann non-parametric estimate of location shifts based on untransformed data is provided with its 90% CI.

In view of the purely safety-oriented study objective and the participation of an adolescent population, it appears acceptable that the blood sampling schedule was not adapted to adequately quantify the kinetics of the rapidly absorbed (tmax <5') and short-lived parent compound BDP which in adition is known to undergo extensive first-pass metabolism.

As stated in the Q&A document of the PKWP dated 03/2020 (item 4.11), truncated AUC0-30min of BDP without charcoal block is however considered a more sensitive measure of pulmonary deposition than AUC0-30min of B17MP, and thus efficacy. Though available BDP data need to be interpreted with caution (as based mainly on three sampling times only), they together with B17MP data may point towards a relevantly lower pulmonary deposition of ICS from the formulation in an adolescent population. The width of the 90%CI appears does not appear to be excessively wide.

- ***Pharmacodynamic parameters***

As mentioned above, the PD analysis set consisted of N=75 patients. Two adolescent patients and three adult patients were excluded from the PK analysis due to quantifiable pre-dose concentrations of formoterol (5.7% to 15.7% of individual Cmax during PK profiling). Reference is made to the section «*Results - Recruitment/ Number analysed*» of this report.

Hypokalaemia is known to be potentially associated with beta-agonist treatment. Results of this study are difficult to interpret due to the important number of haemolytic samples, especially in the adolescent group. Available serum glucose results point towards the fact that formoterol at the supratherapeutic dose administered led to an increase in blood glucose which in two adolescents exceeded the normal range.

Overall, there were no relevant trends over time or between groups in terms of the various cardiovascular parameters assessed.

- ***Pharmacodynamics – Potassium***

Multiple blood samples were haemolysed, thereby relevantly affecting the analysis of potassium serum concentrations. As can be seen from Table 14.2.3.2, this problem predominantly affected the adolescent age group.

The sponsor has therefore defined a set of post-study criteria to determine which single and/or patient potassium results are included in the descriptive statistical analysis and which are excluded. As this approach is considered arbitrary, the conclusions regarding potassium serum

levels and profile of adolescent patients are not considered conclusive by the clinical assessor and therefore not presented in detail in the core of this assessment report. For details, reference is made to chapters 11.6.1 and 11.6.2.1 of the CSR.

- ***Pharmacodynamics – Glucose***

The pharmacodynamics of glucose were studied in serum up to 4h post-dose. It is noted that patients were fasting up to approximately 2h post-dose when a standardises meal was served to all participants. This is most likely the reason for the increase in glucose serum concentrations between the 2h and 4h post-dose measurement time when the glucose result exceeded the upper reference range of 5.9 mmol/L in many participants.

In two adolescents hyperglycaemia was reported prior to food intake already (Table 12). In the immediate post-dosing period, a total of N=6 adult patients of the PD population presented hyperglycaemia, which was however already present upon the pre-dose measurement. Only two adults with pre-dose serum glucose in the normal range showed an increase exceeding the normal range in the post-dose period and prior to food intake.

Table 12: Study participants with post-dose hyperglycaemia (glucose serum concentration >5.9 mmol/L) prior to food intake

pre-dose	20′ post-dose	1h post-dose	2h post-dose	4h post-dose
4.73*	**5.05**	**6.68**	4.96	4.80
4.68	**7.40**	**7.07**	**8.21**	**6.80**
5.41	5.16	**6.03**	**6.17**	**8.87**
4.92	**6.06**	5.87	5.81	**10.2**

* deviation from nominal time greater than the maximum allowed deviation; concentration excluded from descriptive statistics

- ***Pharmacodynamics – parameters based on 24h Holter recordings***

In both age groups, **mean HR** increased from 4h until 12h post-dose, the mean maximum change from baseline being +15 bpm at 10h post-dose for adolescents +8.3 bpm at 4h post-dose for adults (Figure 6).

After discharge from the clinical unit (at 16h and 20h post-dose), the mean HR decreased to below baseline values in both age groups to re-increase on the next morning.

In addition, heart rate averages were calculated from Holter recordings for three sampling intervals (HR0-4h, HR0-12h and HR0-24h).

Overall, the HR profiles presented no relevant differences between the two age groups.

Similarly, **QTcF** and the respective change from baseline was comparable in adolescents and adults with no obvious between-group differences (Figure 7). Individual increases from baseline in QTcF of >30ms were observed in N=4 (10.8%) adolescents and N=12 (36.4%) adults, but none of these resulted in a QTcF of >450ms (males) or >470ms (females).

Figure 6: mean change from baseline in HR (bpm) over time (PD analysis set)

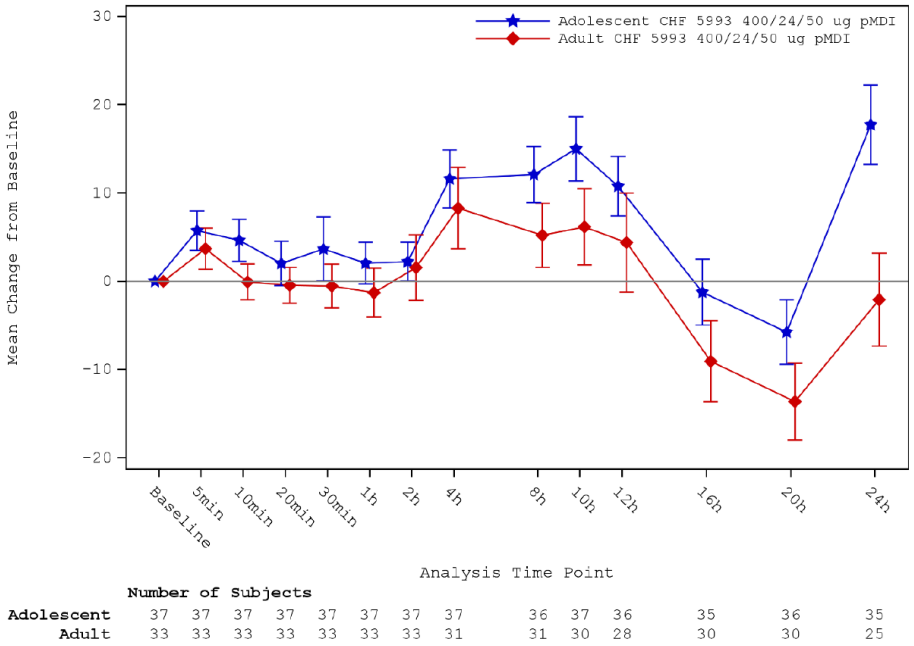
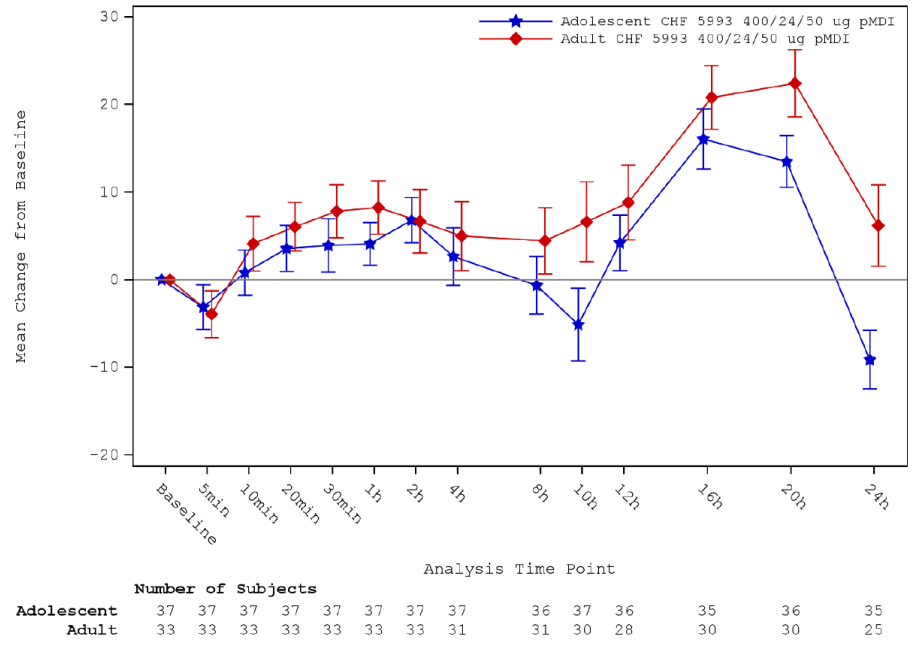


Figure 7: mean change from baseline in QTcF (ms) over time (PD analysis set)



Safety results

Overall, no relevant or new safety signals were identified in the adolescent and adult patients enrolled in this clinical study and administered a single supratherapeutic dose of CHF5993 (nominal dose 400 mcg BDP, 24 mcg FF, and 50 mcg GB).

- ***Treatment-emergent adverse events***

Analyses of safety parameters were based on the safety dataset, defined as all patients who were enrolled and received at least one dose of the investigational medicinal product (CHF5993).

No deaths, other SAEs, or COVID-19-related TEAEs were reported during this study. Overall, a low number of treatment-emergent AEs (TEAEs) were reported. N=3 (3.8%) of adult participants and none of the adolescents reported to have experienced a TEAE. All four (4) TEAEs reported in the 3 adult patients were mild in intensity, required no treatment, resolved before trial end, and were considered to be treatment related (Table 13).

Table 13: Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Safety Set)

Treatment-Emergent Adverse Events (TEAEs)	Adolescents N=40		Adults N=40		Overall N=80	
	n (%)	E	n (%)	E	n (%)	E
Any TEAE	**0**		**3 (7.5)**	**4**	**3 (3.8)**	**4**
General Disorders and Administration Site Conditions	**0**		**1 (2.5)**	**1**	**1 (1.3)**	**1**
Non-cardiac chest pain	0		1 (2.5)	1	1 (1.3)	1
Nervous System Disorders	**0**		**1 (2.5)**	**1**	**1 (1.3)**	**1**
Dysgeusia	0		1 (2.5)	1	1 (1.3)	1
Psychiatric Disorders	**0**		**1 (2.5)**	**1**	**1 (1.3)**	**1**
Anxiety	0		1 (2.5)	1	1 (1.3)	1
Respiratory, Thoracic, and Mediastinal Disorders	**0**		**1 (2.5)**	**1**	**1 (1.3)**	**1**
Cough	0		1 (2.5)	1	1 (1.3)	1

N=number of patients; n=number of patients with event; E=number of events

- ***Physical examination and clinical safety laboratory results***

Results of physical examinations or clinical safety laboratory were not suggestive of any relevant safety related to the administration of the single supratherapeutic dose of CHF5993.

2.3.3. Discussion on clinical aspects

Clinical study CLI-05993CB1-01 is an uncontrolled, open-label, non-randomised clinical pharmacology study comparing the effects of administering a single supratherapeutic dose of medium strength CHF5993 (CHF5993 100/6/12.5 mcg; N=4 consecutive inhalations, resulting in a nominal dose of 400 mcg BDP, 24 mcg FF, and 50 mcg GB) in adolescent (12 to 17 years of age) and adult asthma patients.

The primary objective of the trial was to quantify the total systemic exposure (AUC0-t) to each of the three active ingredients of CHF 5993 as a surrogate of safety. Thereby, confirmation was sought that the use of the commercially available formulation and medium dose strength of CHF 5993 (which so far is approved in adult patients with asthma only) is safe and does not result in an undesirably high exposure to one or more of the active ingredients (BDP, formoterol, GB) in an adolescent asthma population as compared with adult controls.

This objective was achieved. Available data suggest that Cmax as well as AUC0-t of all three analytes remained clearly below the pre-defined limit of 125%, when comparing adolescent and adult exposures after a single dose of CHF5993.

Results of pharmacodynamic parameters appear to confirm this conclusion as no relevant between-group differences or trends over the observation period of the study were reported. It is mentioned in the core of this report, that an inappropriate blood sampling technique (leading to haemolysis of multiple samples) relevantly limits the interpretability of the potassium results, in particular in the adolescent population.

Based on TEAE data, overall, administration of a single dose of medium strength CHF5993 was safe and well tolerated in both age groups.

Therefore, the applicant is planning now to proceed to the 2nd adolescent study defined in the PIP, i.e. study **CLI-05993CB1-02**

Until further study results are available, the applicant is of the opinion that the currently authorised summary of product characteristics (SmPC) does not need to be updated, since the efficacy of CHF5993 pMDI in adolescents with asthma has not yet been established. This can be agreed to.

It is agreed that the PK study under assessment focussed on safety aspects (i.e. total systemic exposure) and that in view of this objective, the start and frequency of sampling were not adapted to reliably assess the **early disposition phase** and measure truncated AUC (AUC0-0.5h) as a measure of **pulmonary deposition**.

However, with all necessary caveats and limitations, the data generated suggest that pulmonary deposition as roughly estimated from AUC0-0.5h was lower in adolescent asthmatics compared with adults for all three active ingredients (point estimator [90%CI]: B17MP[1] 86.7 [69.9;107.7]; formoterol 77.9 [62.4;97.2]; GB 74.3 [58.4;94.4]). This is further confirmed by AUC0-t data of the rapidly absorbed and short-lived parent compound of the ICS component BDP ([35.4 [24.4;51.2]).

This observation is unexpected since adolescents and adults are considered to have a similar airway geometry and range of breathing patters and tidal volumes. There is however a precedent in this respect.

[1] gastrointestinal absorption of swallowed B17MP not negligible and thus also contributing to AUC0-0.5h (in contrast to the parent compound BDP)

Early absorption of the ICS component (but not formoterol) from the applicant's related, fixed-dose **dual combination product** (**CHF1535 BDP/FF 100/6 mcg pMDI**) was previously reported to be lower in adolescent asthma patients as compared with adults (PK study CP08; procedure reference DE/H/0871/001/II/079). In the corresponding pivotal, 12-week superiority study in adolescent asthma patients (CT05), CHF1535 100/6 mcg pMDI was found not to be superior to BDP monotherapy, neither in terms of pulmonary function parameters (primary variable: change from baseline in pre-dose morning PEF), secondary efficacy variables, nor clinical outcome measures. Consequently, this pMDI medicinal product is still **not indicated in adolescents**.

This and the above tentative PK findings raise a concern and should be taken into account when evaluating whether the PIP development programme is still appropriate and when assessing the usefulness of the therapeutic equivalence (TE) study which is planned next under the PIP in adolescents asthma patients (**study 2**, **CLI-05995CB1-02**).

There appears to be a risk that the planned clinical study will not be suitable to detect differences in pulmonary deposition of the individual components between adolescents and adults (if they do exist), because other than dedicated PK studies, such TE studies are known to have notoriously low discriminatory power, even if correctly designed and powered.

3. CHMP overall conclusion and recommendation

Results of clinical study CLI-05993CB1-01 suggest that administration of a single, supratherapeutic dose of medium strength CHF 5993 100/6/12.5 mcg (N=4 consecutive inhalations, resulting in a nominal dose of 400 mcg BDP, 24 mcg FF, and 50 mcg GB) to adolescents (12 to 17 years of age) is safe and well tolerated. Total systemic exposure (AUC0-t) to each of the three active ingredients as a surrogate of safety was lower in adolescents as compared with adults (upper 90%CI <125%). Recorded pharmacodynamic parameters overall endorsed this conclusion.

Thus, the primary objective of clinical study focussing on this safety aspect was achieved.

The applicant's conclusion that the currently authorised summary of product characteristics (SmPC) does not need to be updated is agreed.

However, preliminary data collected in the PK part of this clinical trial suggest that the pulmonary deposition of all three active ingredients of CHF5993 and especially of the ICS component may be lower in adolescents than in adults, with unclear consequences for the product's efficacy in adolescents as compared with adults. The question arises whether the design and objective of the therapeutic equivalence study planned under the PIP (**CLI-05995CB1-02**), comparing the fixed-dose triple combination product (BDP/FF/GB) with a free dual combination (BDP/FF) in male and female adolescent asthma patients, are suitable to clarify this issue. The MAH is recommended to seek scientific advice with PDCO involvement on this matter.

☒ Fulfilled