21 May 2026
EMADOC-1700519818-3236451
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Trimbow

International non-proprietary name: beclometasone / formoterol / glycopyrronium bromide

Procedure No. EMA/VR/0000315173

Note

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

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List of abbreviations

AR	Assessment Report
AUC	Area Under the Curve
AUC_{0-t}	Area Under the Curve from time zero to last quantifiable concentration
AUC_{0-inf}	Area Under the Curve from time zero to infinity
$AUC_{0-30min}$	Area Under the Curve from time zero to 30 minutes
B17MP	Beclometasone-17-monopropionate
BDP	Beclometasone Dipropionate
BELAC	Belgian Accreditation Body
BID	Twice daily
BLQ	Below Limit of Quantification
BMI	Body Mass Index
CARSAF	Clinical Asthma Study with Formoterol
CCI	Commercially Confidential Information
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
C_{max}	Maximum Observed Plasma Concentration
CSR	Clinical Study Report
CYP3A	Cytochrome P450 3A
DHPC	Direct Healthcare Professional Communication
DPI	Dry Powder Inhaler
EC	European Commission
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ERA	Environmental Risk Assessment
EURD	European Union Reference Date
FAMHP	Federal Agency for Medicines and Health Products (Belgium)
FDC	Fixed-Dose Combination
FF	Formoterol Fumarate
GB	Glycopyrronium Bromide

GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMR	Geometric Mean Ratio
HFA-134a	Hydrofluoroalkane Propellant 134a
HL	Hodges–Lehmann estimate
HPLC	High Performance Liquid Chromatography
ICE	Intercurrent Event
ICH	International Council for Harmonisation
INN	International Non-proprietary Name
IR	Incidence Rate
IRR	Incidence Rate Ratio
ISR	Incurred Sample Reanalysis
K_2-EDTA	Dipotassium Ethylenediaminetetraacetic Acid
LABA	Long-Acting Beta$_2$-Agonist
LAMA	Long-Acting Muscarinic Antagonist
LLOQ	Lower Limit of Quantification
LSM	Least Squares Mean
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder
MACE	Major Adverse Cardiovascular Events
MART	Maintenance and Reliever Therapy
MF	Matrix Factor
MS	Medium Strength
NOAEL	No Observed Adverse Effect Level
NOEL	No Observed Effect Level
OC	Other Concern
OIP	Orally Inhaled Product
PAES	Post-Authorisation Efficacy Study
PASS	Post-Authorisation Safety Study
PD	Pharmacodynamic
PE	Point Estimate
PK	Pharmacokinetic
PL	Package Leaflet

PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
QC	Quality Control
R1	Reference Treatment without Spacer
R2	Reference Treatment with Spacer
RE (%)	Relative Error
RMP	Risk Management Plan
SAP	Statistical Analysis Plan
SD	Standard Deviation
SLF	Simulated Lung Fluid
SmPC	Summary of Product Characteristics
$t_{½}$	Terminal Elimination Half-Life
t_{max}	Time to Maximum Plasma Concentration
TEAE	Treatment-Emergent Adverse Event
TRIBE	Post-Authorisation Safety Study
TRIGGER	Phase III Asthma Study
TRIMARAN	Phase III Asthma Study
UHPLC	Ultra-High-Performance Liquid Chromatography
UL	Upper Limit

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Chiesi Farmaceutici S.p.A. submitted to the European Medicines Agency on 26 November 2025 an application for a variation.

The following changes were proposed:

Variation(s) requested		**Type**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II

Extension of indication to include treatment of asthma for Trimbow 88/5/9 mcg dry powder inhaler (DPI), based on existing data from the development of Trimbow 87/5/9 mcg pressurised metered dose inhaler (pMDI) in COPD and Asthma, Trimbow 172/5/9 mcg pMDI in Asthma and Trimbow 88/5/9 mcg DPI in COPD, as well as on new data coming from the PK 2 study (CLI-05993BB1-01) and on the interim results of the ongoing PASS (TRIBE) study in COPD. As a consequence, sections 4.1, 4.2, 4.4, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and Labelling are updated in accordance. Version 11.1 of the RMP has also been submitted.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0167/2024 on the granting of a product-specific waiver covering all subsets of the paediatric population for the inhalation powder formulation.

Information relating to orphan market exclusivity

Similarity

Not applicable

Scientific advice

The MAH received Scientific Advice from the CHMP on design, endpoints and success criteria (EMA/SA/0000162353) in 2024. In addition, the SAWP discussed the development of the DPI formulation in July 2017.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Janet Koenig

Timetable	Actual dates
Submission date	26 November 2025
Start of procedure:	27 December 2025
CHMP Rapporteur's preliminary assessment report circulated on:	20 February 2026
Joint Rapporteur's updated assessment report circulated on:	05 March 2026
Request for supplementary information and extension of timetable adopted by the CHMP on:	23 March 2026
MAH's responses submitted to the CHMP on:	20 April 2026
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on:	07 May 2026
CHMP Rapporteur's updated assessment report on the MAH's responses circulated on:	13 May 2026
CHMP opinion:	21 May 2026

2. Scientific discussion

Introduction

The present application concerns an extension of indication for the dry powder inhaler (DPI) formulation of CHF 5993 (beclometasone dipropionate/formoterol fumarate/glycopyrronium bromide) to the maintenance treatment of asthma in adults not adequately controlled on ICS/LABA therapy. The pressurised metered dose inhaler (pMDI) formulation of CHF 5993 is already authorised for this indication, and the DPI formulation is authorised for chronic obstructive pulmonary disease (COPD).

No new Phase III efficacy studies were conducted with the DPI formulation in asthma. Instead, the development strategy relied on pharmacokinetic (PK) bridging to the authorised pMDI formulation, in accordance with regulatory guidance for orally inhaled products. The approach aimed to demonstrate comparable lung availability (as a surrogate for efficacy) and systemic exposure (as a surrogate for safety), thereby allowing extrapolation from the established clinical efficacy and safety of the pMDI formulation in asthma.

Lung availability

The primary scientific question was whether lung availability of the DPI formulation is not lower than that of the authorised pMDI formulation. In the dedicated PK study (CLI-05993BB1-01), lung availability was assessed using the parent compound beclometasone dipropionate (BDP), together with early exposure parameters ($AUC_{0\text{-}30min}$) for formoterol fumarate (FF) and glycopyrronium bromide (GB). The use of BDP addressed limitations identified in the earlier COPD PK study, where the active metabolite beclometasone-17-monopropionate (B17MP) had been used as a surrogate.

The results demonstrated that the extent of pulmonary exposure ($AUC_{0\text{-}t}$ and $AUC_{0\text{-}30min}$) was not lower with the DPI formulation, thereby supporting comparable lung delivery.

Systemic exposure

The second key question was whether total systemic exposure to the active components is not higher than that of the authorised pMDI formulation. In the PK study CLI-05993BB1-01, total systemic

exposure to B17MP and glycopyrronium bromide (GB) with the DPI formulation was not higher than that of the pMDI formulation showing the highest exposure. For formoterol fumarate (FF), AUC_{0-t} showed an upper confidence limit above the predefined equivalence threshold, whereas C_{max} was comparable between treatments. The overall exposure pattern did not indicate a clinically meaningful increase in systemic exposure.

Notably, in the earlier COPD PK study, higher systemic exposure to GB and FF had been observed with the DPI formulation. These findings raised concerns, particularly regarding GB C_{max}, and led to post-authorisation safety follow-up (PASS TRIBE). In the present PK study, conducted with therapeutic dosing and optimised early sampling, the previously observed marked increases in GB C_{max} were not reproduced. The differences between the two studies are considered attributable to methodological factors, including dose level and sampling design.

Extrapolation

Given that lung availability was not lower with the DPI formulation and systemic exposure was not meaningfully increased, extrapolation from the established efficacy and safety of the authorised pMDI formulation in asthma is considered justified.

Conclusion

The PK findings demonstrate that the DPI formulation delivers adequate pulmonary exposure to BDP, FF and GB, without evidence of reduced lung availability. Although BDP C_{max} was lower with the DPI formulation, AUC_{0-t} was higher, indicating sustained exposure rather than reduced delivery. For inhaled corticosteroids, sustained exposure is considered relevant for anti-inflammatory efficacy.

With regard to systemic exposure, the slight increase in FF AUC_{0-t} should be interpreted in light of the known pharmacology and clinical use of FF. FF-containing combinations are approved for use at higher cumulative daily doses in asthma, including maintenance and reliever therapy regimens. Available clinical data indicate that such dosing is generally well tolerated. Interim data from the ongoing TRIBE study, although preliminary and derived from a COPD population, have not indicated an increased cardiovascular risk with the DPI formulation compared with the pMDI formulation.

Overall, the PK data, the established clinical profile of the pMDI formulation in asthma, and the available safety data provide a consistent evidence base supporting the use of the DPI formulation. The proposed SmPC reflects the same indication, dose and patient population as the authorised pMDI formulation.

2.1. Introduction

2.1.1. Problem statement

Asthma is a chronic inflammatory airway disease associated with a substantial burden in terms of morbidity, impaired quality of life and healthcare utilisation. Despite the availability of inhaled corticosteroid (ICS) and long-acting β2-agonist (LABA) combination therapies, a proportion of adult patients with moderate to severe asthma remain inadequately controlled and continue to experience exacerbations.

For such patients, current treatment guidelines recommend escalation to triple therapy with the addition of a long-acting muscarinic antagonist (LAMA). While single-inhaler triple fixed-dose combinations (FDCs) are available, the choice of inhalation device may limit optimal use in individual patients. In particular, incorrect technique or difficulty coordinating actuation and inhalation with pressurised metered dose inhalers (pMDIs) may compromise drug delivery and clinical effectiveness.

The present application therefore addresses the need to provide an alternative inhalation device for an already authorised triple ICS/LABA/LAMA therapy, allowing treatment individualisation while maintaining established efficacy and safety. The applicant seeks approval of the dry powder inhaler (DPI) formulation of CHF 5993 (medium strength) for the asthma indication already approved for the corresponding pMDI formulation.

2.1.2. About the product

Trimbow (hereafter also referred to as CHF 5993) is a fixed-dose combination medicinal product containing beclometasone dipropionate (BDP), an inhaled corticosteroid with anti-inflammatory activity; formoterol fumarate (FF), a long-acting β2-agonist providing bronchodilation; and glycopyrronium bromide (GB), a long-acting muscarinic antagonist that inhibits cholinergic bronchoconstriction.

The product under assessment is CHF 5993 DPI medium strength, delivering BDP/FF/GB at a metered dose of 100 µg/6 µg/12.5 µg per inhalation. It is administered via the NEXThaler dry powder inhaler as two inhalations twice daily.

CHF 5993 as a pMDI formulation is already authorised in the European Union for the maintenance treatment of asthma in adults not adequately controlled with an ICS/LABA combination and who experienced one or more exacerbations in the previous year (EMEA/H/C/004257/X/0008/G). The DPI formulation of CHF 5993 is already authorised for chronic obstructive pulmonary disease (COPD) (EMEA/H/C/004257/X/0012).

The present application seeks extension of the asthma indication to CHF 5993 DPI medium strength, with no change to the therapeutic indication, dosing regimen or target population compared with the authorised pMDI formulation.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

Trimbow (hereafter and also in the non-clinical documentation referred to as CHF 5993) is a fixed-dose combination medicinal product containing beclometasone dipropionate (BDP), an inhaled corticosteroid with anti-inflammatory activity; formoterol fumarate (FF), a long-acting β2-agonist providing bronchodilation; and glycopyrronium bromide (GB), a long-acting muscarinic antagonist that inhibits cholinergic bronchoconstriction.

The present type II variation application addresses the need to provide an alternative inhalation device for an already authorised triple therapy, allowing treatment individualisation while maintaining established efficacy and safety.

The applicant seeks approval of CHF 5993 DPI MD (the dry powder inhaler formulation of CHF 5993 medium strength (Trimbow 88/5/9 mcg with a nominal dose per actuation of 100/6/12.5 µg/inhalation) for the asthma indication. CHF 5993 as a Pressurised Metered Dose Inhaler (pMDI) formulation is already authorized in the European Union for the maintenance treatment of asthma in adults. CHF 5993 DPI MD is administered via the NEXThaler® dry powder inhaler.

CHF 5993 DPI MD intended for the asthma indication has already been approved in the COPD indication and will be administered in patients with asthma, with the same total daily dose and posology (two inhalations bid) and for the same indication as already approved for the Trimbow pMDI MS formulation.

No new Phase III efficacy studies in asthma were conducted with the dry powder inhaler (DPI) formulation. This variation is based on existing data from the development of CHF 5993 DPI medium strength pMDI in COPD and Asthma, CHF 5993 pMDI high strength (172/5/9 mcg) in Asthma and CHF 5993 DPI medium strength in COPD, as well as on new clinical data coming from the PK 2 study (CLI-05993BB1-01) and on the interim results of the ongoing PASS (TRIBE) study in COPD.

This approach is consistent with the Guideline on the requirements for clinical documentation for orally inhaled products (OIP Guideline, CPMP/EWP/4151/00 Rev. 1), which allows therapeutic equivalence to be demonstrated through appropriate *in vitro* and pharmacokinetic data, without the need for additional confirmatory efficacy studies, where the reference product is authorised in the relevant indication.

The same regulatory approach was applied for the approval of the CHF 5993 DPI formulation for the COPD indication (EMEA/H/C/004257/X/0012), based on pharmacokinetic bridging to the already authorised pMDI formulation. The PK study CCD-05993BA1-01 comparing the DPI and pMDI formulations identified differences in systemic exposure, in particular higher peak exposure for GB with the DPI formulation compared with the pMDI used with a spacer.

While these differences were not considered clinically meaningful in terms of efficacy or short-term safety, the CHMP considered that additional reassurance on long-term cardiovascular safety was necessary, in view of the higher systemic exposure to GB observed with the DPI formulation. This requirement was considered particularly relevant in the COPD population, given the higher baseline cardiovascular risk and the frequent presence of cardiovascular comorbidities, as well as the known class effects of long-acting bronchodilators.

As a consequence, approval of the DPI formulation for COPD was granted with the request to conduct a post-authorisation safety study (PASS) focusing on major adverse cardiovascular events (MACE), in order to further characterise the long-term cardiovascular safety profile of the DPI formulation under real-world conditions (Category 3 PASS). This PASS TRIBE (CLI-05993BA1-05) is ongoing, and interim results are regularly assessed by PRAC. The second interim report, including information available in the period 01 August 2021-30 December 2023, was submitted to EMA on 23 May 2025 (PAM procedure number EMA/PAM/0000274884).

During a PSM in 2021 addressing the planned Type II variation to extend the indication of Trimbow DPI to asthma, the CHMP Rapporteurs highlighted that the pharmacokinetic data generated during the COPD development programme might not be sufficient to support extrapolation to the asthma population. In particular, it was noted that the initial PK study CCD-05993BA1-01 primarily relied on the active metabolite beclometasone-17-monopropionate (B17MP) as a surrogate for lung deposition. While this approach was considered acceptable in the COPD context, the CHMP confirmed in 2023 that, for the asthma indication, assessment of lung deposition should focus on the parent compound BDP, in line with evolving PKWP guidance and the greater relevance of inhaled corticosteroid exposure for asthma control (EMA/SA/0000133869).

Following another CHMP advice in 2024 on design, endpoints and success criteria (EMA/SA/0000162353), another pharmacokinetic bridging study (CLI-05993BB1-01) was conducted to compare lung availability and systemic exposure of CHF 5993 DPI medium strength with CHF 5993 pMDI medium strength, with and without a spacer.

Overall, the development programme is considered to be in line with CHMP guidance and prior scientific advices.

It is noted that Revision 2 of the OIP Guideline (CPMP/EWP/4151/00 Rev. 2) becomes legally effective on 01/02/2026, i.e. after the submission of the present application. Accordingly, the assessment is

primarily based on the guideline version applicable at the time of submission (CPMP/EWP/4151/00 Rev. 1), while taking into account the relevant clarifications and flexibilities reflected in the Scientific Advice provided in 2024.

2.1.4. General comments on compliance with GLP, GCP

The clinical studies submitted in support of this application were conducted in accordance with the principles of GCP, applicable local regulations and the Declaration of Helsinki.

The pharmacokinetic bridging study was conducted as a clinical pharmacology study with appropriate ethical approval, informed consent procedures and quality assurance measures. Study conduct, data collection and analysis were considered acceptable.

Non-clinical studies referenced in support of the application were conducted in compliance with GLP, where applicable, or were derived from previously assessed and accepted development programmes for the authorised pMDI and DPI formulations.

No critical concerns regarding compliance with GLP or GCP were identified from the submitted documentation.

2.2. Non-clinical aspects

2.2.1. Introduction

A non-clinical overview was submitted in support of the extension of the indication.

No new non-clinical toxicology studies have been conducted in support of this application and no amendments of the non-clinical sections of the Summary of Product Characteristics (4.6 and 5.3) are proposed. The applicant refers to all the non-clinical contents of the CHF 5993 COPD dossier (DPI and pMDI) as the studies are also applicable to support the asthma indication.

Sufficient justification for the absence of studies supporting the present variation has been provided.

The only new content relevant to the asthma indication is a re-calculation of the safety margins derived from the original 13-week repeat dose toxicity studies in rats and dogs using CHF 5993 DPI fixed combination formulation (delivering 100+6+12.5 µg/actuation BDP+FF+GB) taking into account the systemic exposure of asthmatic patients instead of COPD patients.

The safety factor calculation was performed for the asthma indication, analogous to the calculation of the safety factors for the CHF 5993 DP dose for COPD approval. The safety factors were calculated based on an allometric dose conversion and systemic exposure to the active substances of the CHF 5993 triple combination in rats, dogs and human asthma patients (using exposure at NOELs and NOAELs and the exposure at the maximum daily clinical inhalation dose).

RAT

Systemic safety margin calculations as AUC at NOAEL

	Rat 13 week AUC_{0-24} at NOAEL		Human Asthma patients simulated AUC_{0-24}[$]	Safety margins Asthma patients (Safety margins COPD patients*)	
	ng.hr/mL		ng.hr/mL	-	
	Male	Female		Male	Female
BDP	n.a.	n.a.	n/a	-	-
B17MP	310	1540	5.55	56 (67)	277 (331)
FF	4.15	4.59	0.418	10 (26)	11 (28)
GB	9.55	11.6	0.366	26 (30)	32 (36)

n/a: not available. [$]$AUC_{0-24h}$: AUC_{0-12h} were simulated using the population PK models developed starting from concentration data collected in TRIMARAN study at steady-state, after inhalation of BDP/FF/GB 400/24/50 mg/day (100/6/12.5 mg/actuation formulation administered *b.i.d*) (Source: Population PK Study Reports [M 5.3.3.5]). AUC_{0-24h} was extrapolated from the simulated AUC_{0-12h}. * Safety margins for COPD patients are based on pMDI clinical CARSAF study.

Systemic safety margin calculations as C_{max} at NOAEL

	Rat 13 week C_{max} at NOAEL		Human Asthma patients simulated C_{max}[#]	Safety margins Asthma patients (Safety margins COPD patients*)	
	ng/mL		ng/mL	-	
	Male	Female		Male	Female
BDP	19.4	21.5	n/a	- (53)	- (58)
B17MP	71.6	219	0.628	114 (105)	349 (323)
FF	1.90	2.38	0.016	119 (112)	149 (140)
GB	2.81	2.97	0.041	68 (61)	72 (64)

n/a: not available. [#]C_{max} extrapolated were simulated using the population PK models developed starting from concentration data collected in TRIMARAN study at steady-state, after inhalation of BDP/FF/GB 400/24/50 mg/day (100/6/12.5 mg/actuation formulation administered *b.i.d*) (Source: Population PK Study Reports [M 5.3.3.5]). * Safety margins for COPD patients are based on clinical CARSAF study.

DOG

Systemic safety margin calculations as AUC

	Dog 13 week AUC_{0-24} at NOAEL		Human Asthma patients simulated $AUC_{0-24}^{\$}$	Safety margins Asthma patients (Safety margins COPD patients*)	
	ng.hr/mL		ng.hr/mL	-	
	Male	Female		Male	Female
BDP	na	na	n.a	- (-)	- (-)
B17MP	13.9	14.7	5.55	2.5 (3)	2.6 (3.2)
FF	0.878	0.684	0.418	2.1 (5.4)	1.6 (4.2)
GB	2.65	1.63	0.366	7.2 (8.3)	4.4 (5.1)

n/a: not available. $^{\$}AUC_{0-24h}$: AUC_{0-12h} were simulated using the population PK models developed starting from concentration data collected in TRIMARAN study at steady-state, after inhalation of BDP/FF/GB 400/24/50 mg/day (100/6/12.5 mg/actuation formulation administered *b.i.d*) (Source: Population PK Study Reports [M 5.3.3.5]). AUC_{0-24h} was extrapolated from the simulated AUC_{0-12h}. * Safety margins for COPD patients are based on clinical CARSAF study.

Safety margin calculations as C_{max}

	Rat 13 week C_{max} at NOAEL		Human Asthma patients simulated C_{max}#	Safety margins Asthma patients (Safety margins COPD patients*)	
	ng/mL		ng/mL	-	
	Male	Female		Male	Female
BDP	1.59	1.91	n.a.	- (4.3)	- (5.2)
B17MP	5.87	6.80	0.628	9 (8.6)	11 (10)
FF	0.275	0.221	0.016	17 (16.2)	14 (13)
GB	0.367	0.345	0.041	9 (8)	8 (7.5)

n/a: not available. $^{\#}C_{max}$ extrapolated were simulated using the population PK models developed starting from concentration data collected in TRIMARAN study at steady-state, after inhalation of BDP/FF/GB 400/24/50 mg/day (100/6/12.5 mg/actuation formulation administered *b.i.d*) (Source: Population PK Study Reports [M 5.3.3.5]). * Safety margins for COPD patients are based on pMDI clinical CARSAF study.

Two new reports in section 4.2.2.7 are included to support the present application

1. A preclinical study was performed to evaluate the PK profile in rat of the triple combination after administration by inhalation either as CHF5993 pMDI and CHF5993 DPI to possibly understand and explain the effect of these two dosage forms and formulation properties on plasma PK profile in human (PRECL-DISCOVERY RP-0081). The results of this study showed that mean plasma profile for FF and GB were almost similar after administration of DPI and pMDI. BDP plasma AUClast values resulted to be comparable between the two formulations, suggesting similar overall exposure, but an earlier Tmax and higher Cmax was observed when administered as pMDI in respect to DPI. Tmax was 0.27 and 0.33 h for pMDI and DPI, respectively, and Cmax was 11.6 and 7.41 ng/mL for pMDI and DPI, respectively.

Klinische PK: for FF, a higher total systemic exposure was observed following administration of the DPI formulation compared with the reference pMDI formulation with spacer.

2. A hypothesis for this behaviour is related to the different solubility and dissolution rate for pMDI in respect to DPI, in particular for BDP, and for this reason an In-Vitro test to evaluate the apparent solubility (Sapp) in simulated lung fluid (SLF) of the three components in the formulation was performed (RECL-DISCOVERY RP-00803). Due to their very high solubility, the pharmacokinetics of GB and FF are not affected and are expected to remain consistent between the DPI and pMDI formulations. Conversely, the BDP solubility is likely to play a role in the pharmacokinetics and differences in BDP solubility between the two formulations are anticipated to be mirrored in the pharmacokinetic behaviour.

2.2.2. Ecotoxicity/environmental risk assessment

The applicant provided a justification for not submitting a detailed ERA because no increase of the PECsw value in Phase I is expected.

Table 1: Summary of main study results: Phase I

Substance (INN/Invented Name):	Formoterol fumarate dihydrate		
CAS-number (if available):	183814-30-4		
PBT/vPvB screening			
Study type	Test protocol	Result	Conclusion
Bioaccumulation potential- log Kow	OECD 107	-0.02 at pH 7	Potential PBT: N
PBT/vPvB assessment			
Property	Parameter	Result	Conclusion
Bioaccumulation	log k_{ow}	-0.02 at pH 7	not B
	BCF_{Kgl}	Not available	
Persistence	Ready biodegradability	Not available	
	$DT_{50,X}$ at 12°C	Not available	
Toxicity	$NOEC_{aquatic}$ C, M, R STOT RE 1 or 2	Not available	
PBT/vPvB statement:	Formoterol fumarate dihydrate is considered to be not PBT, nor vPvB		

Phase I			
Parameter	Value	Unit	Conclusion
$PEC_{sw, default}$	0.00012	µg/L	≥ 0.01 threshold: *N*
Other concerns (e.g. chemical class)			N

Table 2: Summary of main study results: Phase I

Substance (INN/Invented Name):	glycopyrronium bromide
CAS-number (if available):	51186-83-5

PBT/vPvB screening			
Study type	Test protocol	Result	Conclusion
Bioaccumulation potential- log Kow	OECD 107	-1.35 at pH 7	Potential PBT: N

PBT/vPvB assessment			
Property	Parameter	Result	Conclusion
Bioaccumulation	log k_{ow}	-1.35 *at pH* 7	not B
	BCF_{Kgl}	Not available	
Persistence	Ready biodegradability	Not available	
	$DT_{50,water}$ at 12°C	Not available	
Toxicity	$NOEC_{aquatic}$ C, M, R STOT RE 1 or 2	Not available	
PBT/vPvB statement:	Glycopyrronium bromide is considered to be not PBT, nor vPvB		

Phase I			
Parameter	Value	Unit	Conclusion
$PEC_{sw,\ default}$	0.00025	µg/L	≥ 0.01 threshold: N
Other concerns (e.g. chemical class)			N

Table 3: Summary of main study results: Phase I

Substance (INN/Invented Name):	beclomethasonmonopropionat
CAS-number (if available):	5534-09-8

PBT/vPvB screening			
Study type	Test protocol	Result	Conclusion
Bioaccumulation potential- log Kow	OECD 107	3.49 at pH 7	Potential PBT: N

PBT/vPvB assessment			
Property	Parameter	Result	Conclusion
Bioaccumulation	log k_{ow}	3.49 *at pH* 7	not B
	BCF_{Kgl}	1.15	Not B
Persistence	Ready biodegradability	Not readily biodegradable	
	$DT_{50,water}$ at 12°C	Parent: 4.1 d TP MetL: 97.7 d	Not P vP
Toxicity	$NOEC_{aquatic}$ C, M, R STOT RE 1 or 2	Not available	
PBT/vPvB statement:	Beclometasondipropionat is considered to be not PBT, nor vPvB		

Phase I			
Parameter	Value	Unit	Conclusion
PEC_{sw}, *default Beclometasonmonopropionat*	0.0036	µg/L	≥ 0.01 threshold: *N*
Other concerns (e.g. chemical class)	Endocrine active		Yes

Table 4: Summary of main study results: Phase II

Phase II Physical-chemical properties and fate			
Study type	Test protocol	Result	Remarks
Aerobic and Anaerobic Transformation in Aquatic Sediment systems Sediment 1 = Clay	OECD 308	$DT_{50,\ water\ 1}$ = 0.176 d $DT_{50,\ sediment\ 1}$ = na $DT_{50,\ whole\ system\ 1}$ = 0.177 d CO_2 = 1.6 % NER_{total} = 19.1 % $NER_{type\ I}$ = na	beclometasonmonpropionat 20 °C CO_2 and NER values at test end
Sediment 2 = Silty clay loam		$DT_{50,\ water\ 2}$ = 1.39 d $DT_{50,\ sediment\ 2}$ = na d $DT_{50,\ whole\ system\ 2}$ = 1.84 d CO_2 = 0.7 % NER_{total} 27.4 % $NER_{type\ I}$ = na %	20 °C CO_2 and NER values at test end
Transformation products		>10% = Y ; 8TP TP1 (max) = 10.1 $DT_{50,water}$ TP1: 45.8 d (20°C)	Met-L at day 14, total system very persistent Met-L, identity unknown

Phase II Aquatic effect studies					
Study type	**Test protocol**	**Endpoint**	**Value**	**Unit**	**Remarks**
Fish, FFLC / Pimephales promelas Beclometasonmonopropionat	OECD FFLC	$NOEC_{growth}$	0.13	µg/L	Mean measured; 286 d (incl. 65 d F1), flow-through, analysis <80%
Phase II Secondary poisoning					
Bioaccumulation Test/ Oncorhynchus mykiss Test 1 = 1 mg/L	OECD 305	$BCF_{KgL,\ 1}$	1.15	L/kg	

Risk characterisation				
Compartment	**PEC**	**PNEC**	**RQ**	**Conclusion**
Surface water	0.0036 µg/L	0.013 µg/L	0.277	No risk
Groundwater	0.0009 µg/L	0.0013 µg/L	0.692	No risk

2.2.3. Discussion on non-clinical aspects

No new non-clinical toxicology studies have been conducted in support of this application and no amendments of the non-clinical sections of the Summary of Product Characteristics (4.6 and 5.3) are proposed. The applicant refers to all the non-clinical contents of the CHF 5993 COPD dossier (DPI and pMDI) as the studies are also applicable to support the asthma indication. This is considered acceptable.

The only new content relevant to the asthma indication is a re-calculation of the safety margins considering the systemic exposure of asthmatic patients instead of COPD patients.

The safety factor calculation was performed for the asthma indication, analogous to the calculation of the safety factors for the CHF 5993 DP dose for COPD approval. The data presented demonstrates that there are overall adequate safety margins and exposures in asthma patients for the active ingredients administered in the CHF 5993 combination. It is noteworthy that the safety margins for asthma patients are comparable to those calculated for COPD patients. Also considering that no new safety concerns have been identified in the newly submitted clinical data, and that the results of the CLI-05993BB1-01 PK study and the available post-marketing data are consistent with the product's known safety profile, the asthma indication extension for CHF 5993 DPI MD, which is already approved for the pMDI formulation, can be approved from a non-clinical point of view.

Notably, a preclinical study was performed to evaluate the PK profile in rat of the triple combination after administration by Nose-Only inhalation either as CHF5993 pMDI and as CHF5993 DPI to understand the effect of the two dosage forms and formulation properties on plasma PK profile in human (PRECL-DISCOVERY RP-0081 and an *In-Vitro* test to evaluate the apparent solubility (Sapp) in simulated lung fluid (SLF) of the three components in the formulation was performed (RECL-DISCOVERY RP-00803).

No risks to the environment are identified. PECsurfacewater for formoterol fumarate dihydrate is below the action limit of 0.01 µg/L. Consequently, a Phase II risk assessment is not required. PECsurfacewater for glycopyrronium bromide is below the action limit of 0.01 µg/L. Consequently, a Phase II risk assessment is not required. Considering the above data from Phase I and Phase II, beclometasondipropionat is not expected to pose a risk to the environment. A bioaccumulation potential is not indicated based on the log KOW < 4.5 for all active substances. A definitive PBT/vPvB assessment is not required. In case the PEC value increases in future variation procedures (higher dosage or regimen) a refinement may be necessary and an OECD 106 will be required.

2.2.4. Conclusion on the non-clinical aspects

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of Trimbow 88/5/9 mcg DPI. Considering the above data, Trimbow 88/5/9 mcg DPI is not expected to pose a risk to the environment.

Overall, the non-clinical data submitted sufficiently characterise the PK profile of Trimbow 88/5/9 mcg DPI in support of this extension of indication in asthma in the adult population.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH

- Tabular overview of clinical studies

Type of study	Study identifier	Location of study report	Objective(s) of the study	Study design and type of control	Test product(s) dosage regimen: Route of administration	Number of subjects/patients	Subjects/ patients	Duration of treatment	Study status; Type of report
PK	CLI-05993BB1-01	M 5.3.1.2	To evaluate the lung availability and the total systemic exposure of BDP/B17MP, formoterol and GB as AUC_{0-t} and C_{max}, after administration of two different formulations of BDP/FF/GB (100/6/12.5 µg) DPI, in comparison with BDP/FF/GB (100/6/12.5 µg) pMDI (with/without spacer)	Phase I, randomised, open-label, single-dose, three-way cross-over, single-centre study	Single doses of: BDP/FF/GB DPI BDP/FF/GB pMDI BDP/FF/GB pMDI with spacer All treatments taken as 4 inhalations/actuations for total daily doses of: BDP 400 µg, FF 24 µg, GB 50 µg	66	Healthy adults	Single dose	Complete; Full

AUC_{0-t} = Area under the concentration-time curve calculated between time 0 and the last quantifiable time point; B17MP = Beclometasone-17-monopropionate; BDP = Beclometasone dipropionate; C_{max} = Maximal plasma concentration; DPI = Dry powder inhaler; FF = Formoterol fumarate; GB = Glycopyrronium bromide; PK = Pharmacokinetic; pMDI = Pressurised metered dose inhaler.

2.3.2. Analytical methods

All analytical methods were developed and validated by the contract research organisation. Determination of the analytical concentrations of BDP, B17MP, FF and GB in human samples was performed using a selective and sensitive liquid chromatography (LC) followed by tandem mass spectrometry (MS-MS) detection method (high performance liquid chromatography [HPLC] or ultra-high-performance liquid chromatography [UHPLC]).

The bioanalytical methods were validated in compliance with the EMA guidance on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009) for precision and accuracy, linearity of the calibration curves, absolute recovery, selectivity, dilution integrity, carry-over and matrix effects. Validation data as well as stability data support the use of the analytical method for the quantification of all the three compounds in human plasma.

Bioanalysis of study samples

Table 5: Sample analysis of study CCD-05993BA1-01 (BDP)

Analyte	BDP
Total numbers of collected samples	6622
Total number of samples with valid results	3311
Total number of reassayed samples[a, b]	31
Total number of analytical runs[a]	33
Total number of valid analytical runs[a]	33
Incurred sample reanalysis	
Number of samples	226
Percentage of samples where the difference between the two values was less than 20% of the mean	98.23%

[a] Without incurred samples.

[b] Due to other reasons than not valid run.

Source: Module 2.7.1, Table 38

Table 6: Sample analysis of study CCD-05993BA1-01 (B17MP)

Analyte	B17MP
Total numbers of collected samples	6622
Total number of samples with valid results	3311
Total number of reassayed samples[a, b]	160
Total number of analytical runs[a]	33
Total number of valid analytical runs[a]	33
Incurred sample reanalysis	
Number of samples	225
Percentage of samples where the difference between the two values was less than 20% of the mean	95.56%

[a] Without incurred samples.

[b] Due to other reasons than not valid run.

Source: Module 2.7.1, Table 39

Table 7: Sample analysis of study CCD-05993BA1-01 (FF)

Analyte	FF
Total numbers of collected samples	8754
Total number of samples with valid results	2919
Total number of reassayed samples[a, b]	17
Total number of analytical runs[a]	26
Total number of valid analytical runs[a]	24
Incurred sample reanalysis	
Number of samples	226
Percentage of samples where the difference between the two values was less than 20% of the mean	82.74%

[a] Without incurred samples.

[b] Due to other reasons than not valid run.

Source: Module 2.7.1, Table 40

Table 8: Sample analysis of study CCD-05993BA1-01 (GB)

Analyte	GB
Total numbers of collected samples	6620
Total number of samples with valid results	3310
Total number of reassayed samples[a, b]	0
Total number of analytical runs[a]	25
Total number of valid analytical runs[a]	25
Incurred sample reanalysis	
Number of samples	224
Percentage of samples where the difference between the two values was less than 20% of the mean	99.55%

[a] Without incurred samples.

[b] Due to other reasons than not valid run.

Source: Module 2.7.1, Table 41

2.3.3. Clinical pharmacology – PK bridging study CLI-05993BB1-01

The present 3-way crossover study was conducted to compare CHF5993 100/6/12.5 µg NEXThaler® DPI to CHF5993 100/6/12.5 µg pMDI HFA-134a (with and without AeroChamber Plus® spacer), by assessing the lung availability of BDP, FF, and GB, and the total systemic exposure to B17MP, FF, and GB, after inhaled administration (4 inhalations). Lung availability was used as a surrogate for efficacy, while total systemic exposure was used as a surrogate for safety in the comparison between DPI and pMDI products.

The primary aim of this study was to demonstrate that the lung availability of CHF5993 100/6/12.5 µg NEXThaler® DPI is not lower than that of the CHF5993 100/6/12.5 µg pMDI HFA-134a (i.e., to demonstrate comparable efficacy) and to demonstrate that the total systemic exposure of CHF5993 100/6/12.5 µg NEXThaler® DPI is not higher than that of the CHF5993 100/6/12.5 µg pMDI HFA-134a (i.e., to demonstrate comparable safety).

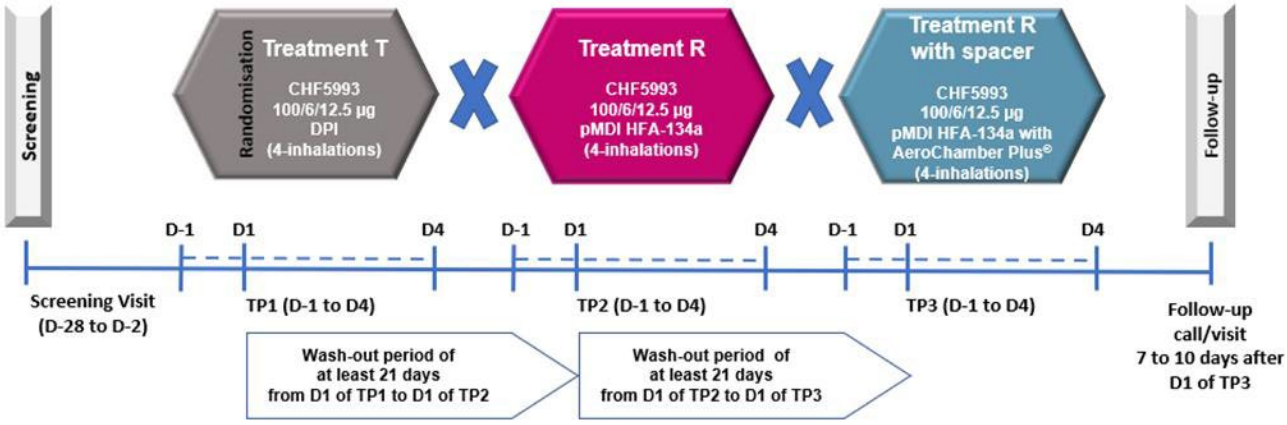
Overall study design and sample size

A single dose, randomised, open-label, 3-way crossover clinical pharmacology study to evaluate the lung availability of beclomethasone dipropionate, formoterol fumarate and glycopyrronium bromide after inhalation of CHF5993 100/6/12.5 µg NEXThaler® 4-inhalations or CHF5993 100/6/12.5 µg pMDI HFA-134a 4-inhalations and the total systemic exposure of beclomethasone 17-monopropionate (active metabolite of beclomethasone dipropionate), formoterol fumarate and glycopyrronium bromide after inhalation of CHF5993 100/6/12.5 µg NEXThaler® 4-inhalations or CHF5993 100/6/12.5 µg pMDI HFA-134a 4-inhalations with and without AeroChamber spacer in healthy volunteers (study identification No. CLI-05993BB1-01, EUDRACT No. 2024-512792-13-00).

Overall study design and sample size

This study had a single-dose, randomised, open-label, 3-way crossover design.

Figure 1: Study design



Source: CSP (Version No. 1.0, dated 28 July 2025), page 38/484

This study was conducted in male and female healthy volunteers because PK studies in healthy subjects are likely to be more sensitive than studies in patients for detecting performance differences between products. Moreover, the potentially confounding influence of variable airway obstruction across study periods usually observed in asthmatic patients is avoided with healthy volunteers.

A total of 66 healthy subjects were planned to be randomised. At least 25 of the 66 subjects were to be males and at least 25 subjects were to be females to ensure gender representation. Recruitment occurred in a CPU authorised to conduct a Phase I study, based on their healthy subjects database.

Since healthy subjects are generally inexperienced in the use of inhaler devices, instructions and training were provided to all participants prior to each administration to ensure correct handling of the DPI and pMDI inhalers and correct execution of the inhalation manoeuvres. For this purpose, DPI training using the In-Check™ DIAL training device together with a DPI placebo inhaler, and pMDI training using the AIM™ (Vitalograph®) device together with a pMDI placebo inhaler, were documented.

All administrations were performed under the supervision of the Investigator or a designated study staff member, and any actual or suspected irregularities during administration were to be recorded in the eCRF.

Inhalation manoeuvres were evaluated for correct execution by the investigator(s) at the time of dosing. For each inhalation manoeuvre, a binary assessment (inhalation performed correctly: yes/no) was recorded in the eCRF. Where applicable, remarks or deviations related to the inhalation manoeuvre were to be documented in the corresponding comment fields.

Organisational structure

Table 9: Study sites

	Name	**Address**	**EU Authority Inspection**	
			Year	**Authority**
Clinical Study Site			FAMHP GCP (June 2025) FAMHP GMP (December 2021) FAMPH GMP questionnaire (2024)	
Bioanalytical Study Site (PK[a])			2024	Belgian GLP Monitoring Authority
Bioanalytical Study Site (PD)	NA	-	-	-
Central Laboratory (cardiac safety[b])			see above	
Clinical Laboratory[c]			2024	BELAC
PK and Statistical Analysis			2012	EMA
Sponsor of the study	Chiesi Farmaceutici S.p.A.	Via Palermo 26/A 43122 Parma Italy	-	-

Source: Module 2.7.1, Table 19

Treatments, test and reference products

A single dose of CHF 5993 corresponding to the maximum daily clinical dose was administered, consisting of four inhalations of CHF 5993 100/6/12.5 µg (total dose: 400 µg BDP, 24 µg FF and 50 µg GB).

As per the allocation based on the randomisation list, subjects were to receive one single dose of each of the following study treatments in a crossover design:

- Treatment T (T): CHF5993 100/6/12.5 µg NEXThaler® DPI;
- Treatment R1 (R1): CHF5993 100/6/12.5 µg pMDI HFA-134a;
- Treatment R2 (R2): CHF5993 100/6/12.5 µg pMDI HFA-134a with AeroChamber Plus® spacer.

All administrations were performed under fasted conditions. Given the inhaled route of administration, food effects on the pharmacokinetic parameters assessed are not expected.

A wash-out period of at least 21 days had to be respected between two consecutive administrations to assure the elimination of the previous dose effect (carry-over effect).

A summary of the study drugs used, including batch numbers and expiry dates, is presented in Table 10.

Table 10: Test and reference product information

Product Characteristics	**Test product**	**Reference product**
Name	CHF 5993 DPI MS (T)	CHF 5993 pMDI MS (R1 without spacer and R2 with spacer)
Strength	BDP/FF/GB 100/6/12.5 µg per inhalation	BDP/FF/GB 100/6/12.5 µg per actuation
Dosage form	Dry powder inhalation	Solution for inhalation
Manufacturer	Chiesi Farmaceutici S.p.A.	Chiesi Farmaceutici S.p.A.
Measured content(s)[a] (% of label claim)	BDP (%): 99 FF (%): 104 GB (%): 102	BDP (%): 89 FF (%): 92 GB (%): 88
Expiry date (Retest date)	December 2025	February 2026
Location of Certificate of Analysis	CSR, Appendix 16.1.6	
Member State where the reference product is purchased from	NA	NA
This product was used in the following trial	PK study CLI-05993BB1-01	

Source: Module 2.7.1, Table 18

Primary objective

- To evaluate the lung availability of BDP, FF, and GB after single-dose administration (4 inhalations) of CHF5993 100/6/12.5 µg NEXThaler® DPI in comparison with CHF5993 100/6/12.5 µg pMDI HFA-134a to demonstrate that the lung availability of CHF5993 100/6/12.5 µg NEXThaler® DPI is not lower than the lung availability of CHF5993 100/6/12.5 µg pMDI HFA-134a.
- To evaluate the total systemic exposure to B17MP, FF, and GB after single-dose administration (4 inhalations) of CHF5993 100/6/12.5 µg NEXThaler® DPI vs. CHF5993 100/6/12.5 µg pMDI

HFA-134a (with or without AeroChamber Plus® spacer) to demonstrate that the total systemic exposure of CHF5993 100/6/12.5 µg NEXThaler® DPI is not higher than the total systemic exposure of CHF5993 100/6/12.5 µg pMDI HFA-134a (with or without AeroChamber Plus® spacer). The comparisons were to be made using the reference treatment (CHF5993 100/6/12.5 µg pMDI HFA-134a with or without AeroChamber Plus® spacer) showing the highest exposure.

Secondary objective

- To evaluate additional PK parameters of B17MP, FF, and GB after administration of CHF5993 100/6/12.5 µg NEXThaler® DPI in comparison with CHF5993 100/6/12.5 µg pMDI HFA-134a (with or without AeroChamber Plus® spacer).
- To evaluate PK parameters of BDP, B17MP, FF, and GB after administration of CHF5993 100/6/12.5 µg pMDI HFA-134a in comparison with CHF5993 100/6/12.5 µg pMDI HFA-134a with AeroChamber Plus® spacer.

PK sampling

BDP/B17MP: In each treatment period, 17 blood samples of 3 mL each were collected on Day 1 and Day 2 into dipotassium ethylene diaminetetraacetic acid [K2-EDTA] tubes for the determination of BDP and B17MP: pre-dose (within 1 h and 30 min), and post-dose at 5, 7, 10, 15, 20, 30, and 45 min, and at 1, 1.5, 2, 4, 6, 8, 12, 16, and 24 h.

FF: In each treatment period, 15 blood samples of 3 mL each were collected on Day 1 and Day 2 into lithium heparin tubes for the determination of FF: pre-dose (within 1 h and 30 min), and post-dose at 5, 7, 10, 15, 20, and 30 min, and at 1, 2, 4, 6, 8, 12, 16, and 24 h.

GB: In each treatment period, 17 blood samples of 2 mL each were collected on Day 1 and Day 2 and two additional blood samples of 2 mL each were collected on Day 3 and Day 4 into lithium heparin tubes for the determination of GB in plasma: pre-dose (within 1 h and 30 min), and post-dose at 5, 7, 10, 15, 20, and 30 min, and at 1, 2, 4, 6, 8, 12, 16, 24, 48, and 72 h.

Primary PK variables

Lung availability:

- BDP: $AUC_{0\text{-}t}$, C_{max}, and t_{max};
- FF and GB: $AUC_{0\text{-}30min}$, C_{max}, and t_{max}.

Total systemic exposure:

- B17MP, FF, and GB: $AUC_{0\text{-}t}$ and C_{max}.

Statistical analyses

All statistical calculations were done with the SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA). Phoenix WinNonlin version 8.4 (Certara, NJ, USA) was used for calculation of PK parameters.

Populations for analysis

The following analysis sets were considered in the statistical analysis:

- Enrolled set: subjects who signed an informed consent to participate in this study and were screened (i.e., who performed at least an assessment).
- Randomised set: subjects who were randomised into this study.
- Safety set: subjects who were randomised and received at least one dose of study treatment.

- PK set: subjects from the safety set, excluding subjects without any valid PK measurement or subjects with important protocol deviations significantly affecting the whole PK evaluation leading to subject exclusion.

Pharmacokinetic data analysis

The estimand associated with the primary objectives was defined by the following attributes (see Table 11)

Table 11: Estimand Associated With the Primary Objectives

Population	Healthy adult volunteers. Further details about the population are provided in Section 9.3.
Treatments	• Single dose of CHF5993 100/6/12.5 µg NEXThaler® DPI (T) vs. single dose of CHF5993 100/6/12.5 µg pMDI HFA-134a (R1); • Single dose of CHF5993 100/6/12.5 µg NEXThaler® DPI (T) vs. single dose of CHF5993 100/6/12.5 µg pMDI HFA-134a with AeroChamber Plus® spacer (R2).
Variables	• **Lung availability:** ○ BDP: AUC_{0-t}, C_{max}, and t_{max}; ○ FF and GB: $AUC_{0-30min}$, C_{max}, and t_{max}. • **Total systemic exposure:** ○ B17MP, FF, and GB: AUC_{0-t} and C_{max}.
Strategy for ICEs/events leading to missing data	See Table 13
Population-level summary	• **Lung availability:** ○ Ratio of AUC_{0-t}, $AUC_{0-30min}$, and C_{max} adjusted geometric means between T and R1; ○ Hodges-Lehmann estimate of location shift for median t_{max} between T and R1. • **Total systemic exposure:** ○ Ratio of AUC_{0-t} and C_{max} adjusted geometric means between T and R1 or between T and R2. Note: The above comparisons were to be made using the reference treatment (CHF5993 100/6/12.5 µg pMDI HFA-134a) showing the highest exposure (R1 or R2).

Source: CSP (Version No. 1.0, dated 28 July 2025), Table 7

The strategy for ICEs and events leading to missing data for the primary analyses targeting this estimand is summarised in Table 12.

Table 12: Intercurrent Events and Events Leading to Missing Data in the Primary Analysis Targeting Estimand

Event	Strategy
Intercurrent events	
Incorrect study treatment intake assessed during the study (before PK concentrations were available); No valid PK measurements; Concentration BLQ at all time points; Non-zero baseline concentration >5% of Cmax; AUC_{0-t} of reference treatment (R1 or R2) lower than 5% of the same group geometric mean AUC_{0-t} (calculated without inclusion of data from the outlying subject) for all the	A principal stratum strategy was applied for each comparison of interest (T vs. R1 or T vs. R2), analyte (BDP, B17MP, FF, and GB) and PK parameter of interest (AUC_{0-t}, $AUC_{0-30min}$, C_{max}, and t_{max}). With this approach, the subject was to be included in the formal statistical comparison for the inferential analysis only in case of no ICE in both TPs. Impacted PK concentrations as of the start of the ICE were to be excluded from descriptive statistics for the subject, analyte, and period with ICE.

four CHF5993 analytes (BDP, B17MP, formoterol, and GB);	
Vomiting or diarrhoea occurring within 40 min (calculated as 2 times B17MP t_{max}, which was expected to be 20 min) after study treatment intake.	Impacted PK parameters were to be excluded from descriptive and inferential analyses for the subject, analyte, and period with ICE. Note, if concentrations were below the limit of quantification at all time points, no PK parameters were to be derived.
Missing PK samples or PK samples with time deviations not allowing for an accurate calculation of the PK parameter of interest (e.g., missing sample at expected tmax).	A principal stratum strategy was to be applied for each comparison of interest (T vs. R1 or T vs. R2), analyte (BDP, B17MP, FF, and GB) and PK parameter of interest (AUC_{0-t}, $AUC_{0-30min}$, C_{max}, and t_{max}). With this approach, the subject was to be included in the formal statistical comparison for the inferential analysis only in case of no ICE in both TPs. No exclusions of PK concentrations were to be performed from descriptive statistics. If the PK sample was taken at the same time as the next PK sample, the sample taken closest to the planned sampling time point was to be used, the other was to be excluded from PK parameter estimation. Impacted PK parameters were to be excluded from descriptive and inferential analyses for the subject, analyte, and period with ICE.
Use of non-permitted medications known as affecting BDP, B17MP, FF, or GB PK concentrations (e.g., inhibitors of organic cation transporter 2 [OCT2] and multidrug and toxin extrusion protein 1 [MATE1] transporters [in case of GB] and strong cytochrome P450 3A enzyme [CYP3A] inhibitors [in case of BDP and B17MP]).	A hypothetical strategy was applied for the calculation of each PK parameter of interest. This meant that all available PK concentrations up to the ICE were used in the calculation of the PK parameter. Considering the time of the concomitant medication intake and the sampling time points affected, a decision was made (before PK concentrations were available) to consider/not consider the PK concentrations after the ICE, if it was expected that the PK parameter was/ was not reliably estimated. Then, the subject was to be included in the formal statistical comparison for the inferential analysis only in case of accurate calculation of the PK parameter in both TPs. Impacted PK concentrations as of the start of the ICE were to be excluded from descriptive statistics for the subject, analyte, and period with ICE. Impacted PK parameters were to be excluded from descriptive and inferential analyses for the subject, analyte, and period with ICE.
Use of non-permitted medications known as not affecting BDP, B17MP, FF, or GB PK concentrations, thus allowing for an accurate calculation of the PK parameter of interest; Vomiting or diarrhoea occurring more than 40 min (calculated as 2 times B17MP tmax, which was expected to be 20 min) after study treatment intake.	A treatment policy strategy was applied for the calculation of each PK parameter of interest. This meant that all available PK concentrations were used in the calculation of the PK parameter. Then, the subject was to be included in the formal statistical comparison for the inferential analysis only in case of accurate calculation of the PK parameter in both TPs. No exclusions of PK concentrations and PK parameter were to be performed from descriptive and inferential statistics.

Events leading to missing data	
Premature study discontinuation	For this event leading to missing data, all available data up to study discontinuation were included in the analysis. No imputation was performed for data missing due to study discontinuation.

Source: CSP (Version No. 1.0, dated 28 July 2025), Table 8

The PK analysis was performed by the PK Department of using standard software (Phoenix WinNonlin version 8.4 (Certara, NJ, USA)). The PK analysis was based on the PK population.

Changes following unblinding: One subject showed a AUC_{0-t} of reference treatment (CHF5993 pMDI with spacer) lower than 5% of the same treatment geometric mean AUC_{0-t} (calculated without inclusion of data from the outlying subject) for two of the four analytes (namely FF and GB). For the other two analytes (i.e., BDP and B17MP), plasma levels were also low with a AUC_{0-t} about 11-12% of the same treatment geometric mean AUC_{0-t} (calculated without inclusion of data from the outlying subject). Per Section 2.1.3 in the SAP, this subject could have been excluded from analyses only if AUC_{0-t} would have been lower than 5% of the same group geometric mean AUC_{0-t} (calculated without inclusion of data from the outlying subject) for all the four CHF5993 analytes (i.e., BDP, B17MP, FF, and GB). It was decided to perform a post hoc analysis, to explore the impact of this subject on statistical analysis result. This post hoc analysis consisted in excluding this subject, for all analytes, from inferential PK statistical analysis for the T vs. R2 and R1 vs. R2 comparisons.

Inferential statistical PK analysis: BDP, B17MP, FF and GB parameters were compared using analysis of variance (ANOVA) and a corresponding non-parametric test for t_{max}.

Subject disposition and demographic

In total, 66 subjects were randomised to one of the three treatment sequences: 22 subjects in each treatment sequence.

Overall, 64 (97.0%) of the randomised subjects completed the study. In total, 2 (3.0%) randomised subjects prematurely discontinued from the study, of whom 1 (1.5%) subject withdrew consent and 1 (1.5%) subject discontinued due to other reason.

- 1 Subject withdrew consent in the wash-out period of TP1, 11 days after administration of CHF5993 100/6/12.5 µg pMDI HFA-134a using the AeroChamber Plus® spacer in TP1 due to subject logistical reason.
- 1 Subject discontinued in the wash-out period of TP2, 15 days after administration of CHF5993 100/6/12.5 µg pMDI HFA-134a in TP2 due to missed dosing. There was no possibility to catch up.

In total, 65 subjects received CHF5993 100/6/12.5 µg NEXThaler® DPI (T), 65 subjects received CHF5993 100/6/12.5 µg pMDI HFA-134a (R1), and 65 subjects received CHF5993 100/6/12.5 µg pMDI HFA-134a using the AeroChamber Plus® spacer (R2).

The majority of the subjects were white (95.5%) and female (56.1%). The subject's mean (SD) age was 40.7 (8.7) years. Their mean (SD) BMI was 24.65 (2.83) kg/m2. There were no relevant differences seen in demographic data between the treatment sequences.

Primary pharmacokinetic analysis

Important protocol deviations were reported in 8 (12.1%) of the 66 randomised and treated subjects, of which 6 (9.1%) subjects had important protocol deviations leading to the exclusion of PK parameters from the PK set.

The important protocol deviations leading to exclusion from the PK set were:

- Assessment performed out of allowed time window in 2 (3.0%) subjects: 1 Subject had the PK sampling for GB at 72 h post-dose performed out of the allowed window on Day 4 of TP3; 1 Subject had the PK sampling for GB at 72 h post-dose performed out of the allowed window on Day 4 of TP2;
- Visit not performed in 2 (3.0%) subjects: 1 Subject had the visit on Day 4 of TP2 not performed. The subject was not able to come to the unit due to personal circumstances;1 Subject had the visit on Day 4 of TP3 not performed. The subject was ill and was not able to perform this visit;
- Assessment not performed in 1 (1.5%) subject: 1 Subject had the PK sampling for B17MP, BDP, FF, and GB at 5 min and 7 min post-dose not performed on Day 1 of TP2. Due to difficult blood sampling no blood was collected at 5 min and 7 min post-dose.
- Assessment sample collection procedure not correct in 1 (1.5%) subject: For 1 Subject the PK sampling for FF at 16 h post-dose had haemolysis scale higher than 2% on Day 2 of TP2.

All other important protocol deviations observed during the study, not leading to exclusion from PK set, were related to assessment performed out of allowed time window (in 2 [3.0%] subjects).

Incorrect inhalations were reported in 2 (3.0%) subjects:

- 1 Subject was reported with the appearance of a small cloud at the top of the inhaler during the first inhalation of the study drug in TP1;
- 1 Subject puffed twice during the third inhalation of the study drug in TP2. Therefore, no fourth inhalation of the study drug in TP2 was done.

Both incorrect inhalations did not lead to data exclusion from the analysis.

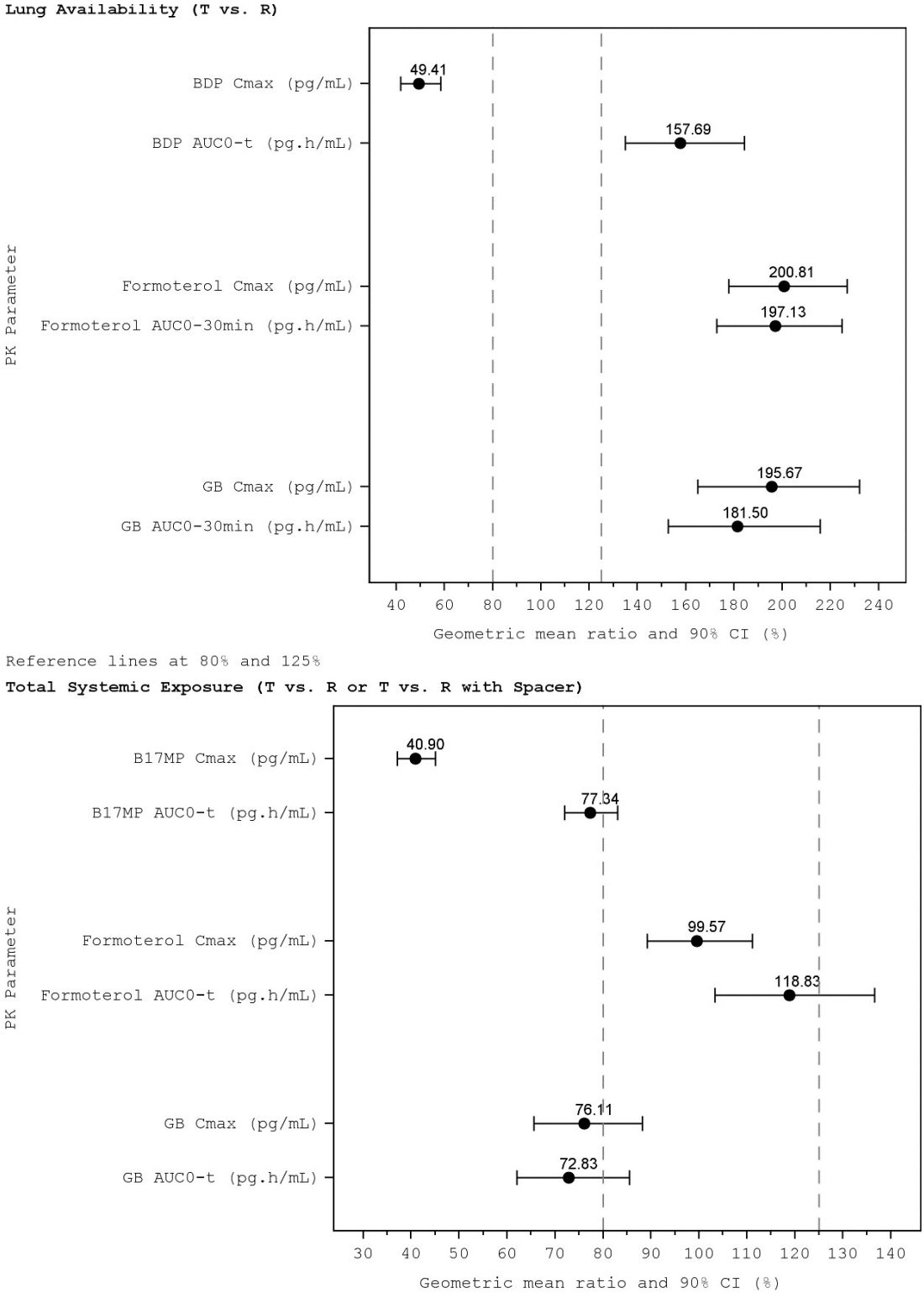
Results of the inferential statistics for BDP, B17MP, FF and GB are presented in Table 13 below.

Table 13: Statistical Evaluation of Primary PK Variables

Lung Availability				
PK parameter (unit)	**n**	**CHF5993 100/6/12.5 µg NEXThaler® DPI (T)**	**CHF5993 100/6/12.5 µg pMDI HFA-134a (R1)**	**T vs R1**
		Geometric LSM[b]	**Geometric LSM[b]**	**PE (90% CI)[a]**
BDP				
Cmax (pg/mL)	64	1119	2264	49.41 (**41.81**; 58.40)
tmax (h)	64	0.08	0.08	0.00 (0.00; 0.00)
AUC0-t (pg.h/mL)	64	445	282	157.69 (**134.9**1; 184.33)
FF				
Cmax (pg/mL)	65	52.7	26.2	200.81 (**177.79**; 226.80)
tmax (h)	65	0.12	0.12	0.00 (-0.03; 0.00)
AUC0-30min (pg.h/mL)	65	15.6	7.94	197.13 (**172.88**; 224.78)
GB				
Cmax (pg/mL)	64	32.8	16.8	195.67 (**165.04**; 231.99)
tmax (h)	64	0.08	0.08	0.00 (-0.02; 0.00)
AUC0-30min (pg.h/mL)	63	10.9	6.01	181.50 (**152.72**; 215.71)

Total Systemic Exposure				
PK parameter (unit)	**n**	**CHF5993 100/6/12.5 µg NEXThaler® DPI (T)**	**CHF5993 100/6/12.5 µg pMDI HFA-134a Without (R1) or With AeroChamber Plus® Spacer (R2)[c]**	**T vs. R1 or R2[c]**
		Geometric LSM[b]	**Geometric LSM[b]**	**PE (90% CI)[a]**
B17MP				
Cmax (pg/mL)	65	534	1304	40.90 (37.10; **45.09**)
AUC0-t (pg.h/mL)	63	2776	3590	77.34 (72.04; **83.04**)
FF				
Cmax (pg/mL)	64	52.8	53.0	99.57 (89.20; **111.15**)
AUC0-t (pg.h/mL)	63	107	90.4	118.83 (103.38; **136.59**)
GB				
Cmax (pg/mL)	64	32.8	43.1	76.11 (65.64; **88.24**)
AUC0-t (pg.h/mL)	59	210	288	72.83 (62.02; **85.53**)

Figure 2: Forest Plot of the Results of the Linear Model for Primary PK Parameters



Source: CSP (Version No. 1.0, dated 28 July 2025), pages 13-14/484

In summary,

- Lung availability (C_{max} and AUC_{0-t} for BDP; C_{max} and $AUC_{0-30min}$ for FF and GB) was higher after inhalation of CHF5993 100/6/12.5 µg NEXThaler® DPI compared with CHF5993 100/6/12.5 µg pMDI HFA-134a for all primary PK variables, with the lower limit of the 90% CI of GMR higher than 80%, except for BDP C_{max}, for which the 90% CI of GMR was lower than 80% (41.81%-58.40%). Therefore, comparable efficacy between CHF5993 100/6/12.5 µg NEXThaler® DPI and CHF5993 100/6/12.5 µg pMDI HFA-134a was demonstrated for FF and GB C_{max} and $AUC_{0-30min}$, as well as for BDP AUC_{0-t}, but not for BDP C_{max}.
- No shift in t_{max} was observed for BDP, formoterol, and GB between all treatments.
- Total systemic exposure (C_{max} and AUC_{0-t} for B17MP, FF, and GB) was lower or comparable after inhalation of CHF5993 100/6/12.5 µg NEXThaler® DPI compared with the reference treatment with the highest exposure (CHF5993 100/6/12.5 µg pMDI HFA-134a with or without the AeroChamber Plus® spacer) for all primary PK variables, with the upper limit of the 90% CI of GMR lower than 125%, except for FF AUC_{0-t}, for which the upper limit of 90% CI of GMR was above 125% (136.59%). Therefore, comparable safety between CHF5993 100/6/12.5 µg NEXThaler® DPI and reference pMDI treatment was demonstrated for B17MP and GB AUC_{0-t} and C_{max}, as well as for FF Cmax, but not for FF AUC_{0-t}.

Post-hoc analysis

A post-hoc analysis excluding one subject with AUC_{0-t} of reference treatment (R2) considerably below the same treatment's geometric mean AUC_{0-t} (<5% for FF and GB and about 11 to 12% for BDP and B17MP) from the T vs. R2 comparison showed lower PEs for C_{max} and AUC_{0-t} (95.01% and 110.75%, respectively) and less wide 90% CIs (Table 14). In this post hoc analysis, the upper limit of the 90% CI for AUC_{0-t} comparing T vs. R2 was below 125.00% (118.27%).

Table 14: Statistical comparison of PK parameters for FF between T and R2 (PK Set)

PK parameter (unit)	**n**	**CHF 5993 DPI MS (T)**	**CHF 5993 pMDI MS with spacer (R2)**	**T vs. R2**	
		Geometric LSM[a]	Geometric LSM[a]	PE (90% CI)[b]	Intra-subject CV (%)
C_{max} (pg/mL)	64	52.8	53.0	99.57 (89.20; 111.15)	38.6
Post-hoc analysis C_{max} (pg/mL)	63	52.6	55.3	95.01 (88.07 ; 102.50)	25.9
AUC_{0-t} (pg.h/mL)	63	107	90.4	118.83 (103.38; 136.59)	49.4
***Post-hoc* analysis** AUC_{0-t} (pg.h/mL)	62	107	96.4	110.75 (103.72 ; **118.27**)	22.1
$AUC_{0-\infty}$ (pg.h/mL)	48	117	110	106.77 (98.55; 115.68)	23.4
$t_{1/2}$ (h)	57	7.26	7.77	93.38 (84.46; 103.25)	32.9

a For tmax, the median is displayed.

b Point estimate and 90% CI of the adjusted GMRs of log-transformed parameters from the linear model in %, except for tmax, where the Hodges-Lehmann non-parametric estimate of location shifts based on untransformed data is provided with its 90% CI.

Source: CSR, Table 14.2.2.12 and PK 2 study CSR, Table 14.2.2.12.1

Applicant's justification for lower BDP C_{max} with the DPI formulation

Differences were observed for BDP following administration of CHF 5993 DPI MS compared with the reference pMDI formulation (without spacer). In particular, in the lung-availability (efficacy) comparison T vs R1, the lower bound of the 90% confidence interval for BDP C_{max} was below 80% (90% CI 41.81; 58.40), whereas the geometric mean ratio for BDP AUC_{0-t} was 157.69% (90% CI 134.91; 184.33), i.e. above 80%.

The Applicant notes that average plasma concentrations of BDP within the first 15 minutes post-dose were higher with the DPI. This is interpreted as indicating that the initially lower BDP C_{max} observed with the DPI formulation is transient.

The Applicant attributes the lower C_{max} to formulation-related differences in dissolution characteristics. Due to the low solubility of BDP, the crystalline form delivered by the DPI formulation is hypothesised to dissolve more slowly in the lung lining fluid than the predominantly amorphous form delivered by the pMDI formulation. This hypothesis is supported by in vitro dissolution studies conducted in simulated lung fluid, which indicate slower dissolution kinetics for BDP from the DPI formulation. According to the Applicant, this may result in lower peak plasma concentrations but more sustained systemic exposure compared with the pMDI formulation.

In contrast, the Applicant states that the high solubility of the crystalline forms of FF and GB ensures rapid dissolution, which is consistent with the absence of relevant differences in *in vivo* pharmacokinetics for these components between the two formulations.

The Applicant further argues that the clinical relevance of the observed mismatch between BDP C_{max} and AUC_{0-t} should be interpreted in light of the pharmacological role of inhaled corticosteroids. BDP is described as a prodrug intended for long-term management of chronic asthma, with its primary effect occurring locally in the lung airways. The Applicant considers that the non-inferior BDP AUC_{0-t} indicates that the total amount of inhaled corticosteroid delivered to the site of action is not reduced with the DPI formulation.

Finally, the Applicant notes that inhaled corticosteroids exert sustained therapeutic effects with regular daily use and that C_{max} is a short-lived and variable parameter in repeated-dose regimens. Given the generally flat dose–response relationship for inhaled corticosteroids over logarithmic dose ranges, the Applicant concludes that the observed difference in BDP C_{max} is unlikely to be clinically meaningful and does not raise concerns regarding lung availability or clinical efficacy.

Applicant's justification for higher FF AUC_{0-t} with the DPI formulation

Table 15: Statistical Assessment of Formoterol PK Parameters - T vs. R2 (PK Set)

PK Parameter (unit)	n	CHF5993 100/6/12.5 µg NEXThaler® DPI (T)	CHF5993 100/6/12.5 µg pMDI HFA-134a With AeroChamber Plus® Spacer (R2)	T vs. R2	
		Geometric LSM[b]	Geometric LSM[b]	PE (90% CI)[a]	Intra-subject CV (%)
C_{max} (pg/mL)	64	52.8	53.0	99.57 (89.20; 111.15)	38.6
AUC_{0-t} (pg.h/mL)	63	107	90.4	118.83 (103.38; 136.59)	49.4
$AUC_{0-\infty}$ (pg.h/mL)	48	117	110	106.77 (98.55; 115.68)	23.4
$t_{1/2}$ (h)	57	7.26	7.77	93.38 (84.46; 103.25)	32.9

n=number of subjects with valid data in both treatment periods; LSM=least square means; PE=point estimate; CI=confidence interval; CV=coefficient of variation

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

[b] For t_{max}, the median is displayed.

Source: Table 14.2.2.12

A higher systemic exposure to FF was observed following administration of CHF 5993 DPI MS compared with the reference pMDI treatment associated with the highest exposure (R2). The point estimate for the geometric mean ratio was 118.83%, with an upper limit of the 90% confidence interval exceeding the conventional upper bioequivalence limit (103.38; 136.59).

The Applicant states that this finding was largely driven by a single subject who exhibited unusually low plasma concentrations of all analytes following reference treatment R2, rather than reflecting a consistent increase in systemic exposure with the DPI formulation. In a post-hoc analysis excluding this subject, the upper limit of the 90% confidence interval for FF AUC_{0-t} (Test vs. R2) fell below the predefined threshold of 125%.

To support the lack of clinical relevance of the observed difference, the Applicant refers to clinical safety data for high and repeated doses of FF. In particular, the fixed-dose combination CHF 1535 pMDI MS (BDP/FF 100/6 µg) is approved for use as both maintenance and reliever therapy (MART), with a maximum daily dose corresponding to 48 µg of FF. A dedicated randomised, placebo-controlled crossover study in adult patients with asthma assessed the tolerability of repeated high-dose administration of CHF 1535 pMDI MS or FF pMDI over one hour. In this study, increases in heart rate were modest, QTc prolongation did not exceed clinically relevant thresholds, and metabolic parameters remained within acceptable limits. Both treatments were reported to be well tolerated at high doses.

In addition, the Applicant considers interim data from the ongoing TRIBE post-authorisation safety study in COPD to be relevant for the assessment of potential cardiovascular risks associated with FF exposure. Although primarily designed to address long-term cardiovascular safety concerns related to the DPI formulation, including those associated with GB, the Applicant argues that the TRIBE study will also provide reassurance regarding the clinical relevance of the higher FF AUC_{0-t} observed in the PK study CLI-05993BB1-01. Interim analyses have not indicated an increased risk of major adverse cardiovascular events for DPI compared with pMDI users.

On this basis, the Applicant concludes that the higher FF AUC_{0-t} observed with the DPI formulation is not clinically relevant and does not raise safety concerns.

2.3.4. Discussion on clinical pharmacology

Clinical pharmacology programme

In line with the OIP Guideline, the Applicant has followed a stepwise development approach, progressing from *in vitro* studies (Step 1) to pharmacokinetic (PK) studies (Step 2). Results of the *in*

vitro studies have already been assessed in the context of EMEA/H/C/004257/X/0012 and are therefore not provided in this report.

According to the OIP Guideline, Step 2 comprises pharmacokinetic studies designed to compare pulmonary deposition and total systemic exposure of the test product with those of the reference product. PK endpoints are generally considered valid surrogate markers for both efficacy and safety, as they are more sensitive than pharmacodynamic or clinical endpoints and therefore increase the likelihood of detecting potential differences between products.

Accordingly, the applicant has conducted a pharmacokinetic bridging study (CLI-05993BB1-01) to compare lung availability and systemic exposure of CHF 5993 DPI with CHF 5993 pMDI, with and without a spacer.

It is noted that an earlier pharmacokinetic study (CCD-05993BA1-01) conducted for the approval of CHF 5993 DPI 5993 in COPD primarily relied on the active metabolite B17MP as a surrogate for lung deposition of the inhaled corticosteroid component. During a PSM with the CHMP Rapporteurs in 2021 it was clarified that, for the asthma indication, assessment of pulmonary deposition should focus on the parent compound BDP, rather than on its active metabolite B17MP. This is in line with previous PKWP guidance, as BDP more directly reflects lung deposition following inhalation, whereas B17MP represents a composite of pulmonary and systemic conversion and is therefore less specific as a surrogate for local lung availability. On this basis, the CHMP advised in 2023 that additional pharmacokinetic data were required (EMA/SA/0000133869), specifically designed to characterise lung deposition of BDP using early and intensive sampling, and to allow a robust comparison between the DPI and pMDI formulations. This requirement led to the conduct of the new PK study CLI-05993BB1-01.

In the Scientific Advice provided in 2024 (EMA/SA/0000162353), CHMP also noted that, while charcoal blockade is generally recommended to differentiate pulmonary from gastrointestinal contribution for orally inhaled products, it is not mandatory in all cases. In this context, the CHMP advised that a direct three-way crossover comparison of CHF 5993 DPI versus CHF 5993 pMDI used with and without a spacer may provide sufficient information on both lung deposition and total systemic exposure without the need for charcoal blockade. For BDP, charcoal blockade was not considered essential, as gastrointestinal absorption following inhalation is negligible and lung deposition is best assessed using the parent compound with early and intensive pharmacokinetic sampling. For FF and GB, early partial exposure parameters, such as $AUC_{0-30min}$, together with adequately characterised C_{max} supported by intensified early sampling, were considered acceptable surrogates for pulmonary exposure.

Further, it was agreed that, for the purpose of assessing pulmonary deposition as a surrogate for efficacy, the lower equivalence margin of 80% is the critical parameter. This agreement was based on the premise that reduced pulmonary deposition of the test product compared with the reference product (without spacer) could translate into reduced local efficacy, whereas moderately higher pulmonary deposition would not be expected to result in a clinically relevant improvement in efficacy, given the established dose–response characteristics of the active substance(s) within the approved therapeutic range.

Furthermore, an increase in pulmonary deposition would primarily raise considerations related to systemic exposure and safety rather than efficacy. These aspects are addressed separately through the assessment of total systemic exposure, applying the conventional upper bioequivalence limit of 125% to ensure that systemic safety of the test product is not inferior to that of the reference product (with or without spacer, whichever results in the higher systemic exposure).

Overall, the development programme is considered to be in line with prior CHMP scientific advice.

Bioanalytical method

All bioanalytical analyses submitted within this application were performed at the same certified bioanalysis facility. It was confirmed that the bioanalytical unit is a GLP-certified facility, and that the analytical work was conducted in accordance with applicable standards, including internal standard operating procedures, ICH GCP E6, the EMA GCP Inspectors Working Group reflection paper for laboratories performing analysis of clinical trial samples, the EMA Guideline on Bioanalytical Method Validation and ICH M10.

Validated LC–MS/MS or UHPLC–MS/MS methods were used for the determination of BDP, its active metabolite B17MP, FF and GB in acidified lithium-heparinised human plasma. Representative chromatograms were provided for all analytes, and selectivity against relevant co-medications and metabolites was demonstrated.

For all four analytes, the validation data demonstrate adequate sensitivity, precision and accuracy over the relevant calibration ranges, including at the lower limit of quantification. Within- and between-run precision and accuracy fulfilled the predefined acceptance criteria, and no relevant carry-over was observed. Matrix effects were systematically assessed, including haemolysed and hyperlipidaemic plasma, and were shown not to adversely affect analytical performance within the validated conditions. Extraction recovery was consistent and comparable between analytes and their respective internal standards.

Long-term stability of study samples was appropriately addressed. The maximum storage duration of incurred samples was covered by validated long-term frozen stability data for all analytes, and additional stability assessments (including freeze–thaw stability, benchtop stability, processed sample stability and incurred sample stability) confirmed that the analytes remained stable under the applied storage and handling conditions. Where deviations or outliers occurred during method validation, these were adequately documented, justified and assessed as not having an impact on the integrity or reliability of the analytical results.

A limited number of study samples were reassessed for reasons other than invalid analytical runs, as explicitly indicated in the bioanalytical reports. All analytical runs met the predefined acceptance criteria and no runs were rejected. These reassessments were conducted in accordance with predefined procedures and were not driven by unexpected concentration values, analytical failures, or post-hoc considerations related to the pharmacokinetic results.

Incurred sample reanalysis was performed for a sufficient number of samples for all analytes and demonstrated reproducibility of the analytical methods. ISR results were used exclusively to assess method performance and were not used for pharmacokinetic evaluation.

Overall, the bioanalytical methods used for the determination of BDP, B17MP, FF and GB are considered adequately validated and suitable for the intended pharmacokinetic analyses. No concerns are raised regarding the validity, integrity or reliability of the bioanalytical data generated for this application.

Study design

Study CLI-05993BB1-01 was designed as a single-dose, randomised, open-label, three-way crossover study in healthy volunteers, comparing the DPI formulation with the pMDI formulation used with and without a spacer. This design is appropriate and in line with the OIP Guideline (CPMP/EWP/4151/00 Rev. 2), as it allows within-subject comparisons of lung availability and systemic exposure while controlling for inter-individual variability.

The selection of pharmacokinetic parameters is appropriate for the objectives of the study. Lung availability is assessed using parent compound BDP and early exposure metrics ($AUC_{0\text{-}30min}$) for the bronchodilator components FF and GB, supported by dense early sampling. Total systemic exposure is

assessed using established parameters (AUC_{0-t} and C_{max}) for all relevant analytes (B17MP, FF and GB). The crossover design and washout periods are adequate to minimise carry-over effects.

Overall, the study design is considered appropriate to support pharmacokinetic bridging between the DPI and pMDI formulations. The design adequately addresses the primary regulatory questions related to lung availability (relevant for efficacy) and systemic exposure (relevant for safety).

Study sites and GCP-inspections

For the clinical study site, a GCP inspection by the Belgian authority (FAMHP) is reported as having taken place in June 2023. According to the information provided, the inspection concluded with no critical or major findings, and only minor observations not impacting the validity or reliability of the data. While no inspection report was submitted, the outcome as described is considered reassuring. Therefore, no concerns remain regarding GCP compliance that would affect the integrity of the clinical data.

Representative batches

A single batch of the reference product and a single batch of the test product were used. The Applicant clarified that both batches were commercial batches taken from routine production close to the start of the PK study. The test DPI batch was 8–11 months old during the study and the reference pMDI batch was 7–10 months old, both within their approved shelf life. The *in vitro* performance of the clinical batches was compared with more than 200 commercial batches manufactured over several years. For both products, FPM and MDD values for BDP, FF and GB were within the relevant limits and within ±15% of the commercial batch means. Stability data were stated to show no significant change up to expiry. Overall, the clinical batches are considered sufficiently representative of commercial production for the purpose of the PK comparison.

Statistical methods

Standard methods and software were used for the calculation of PK variables.

Overall, the statistical methodology is acceptable for a 3-way crossover PK bridging programme, and the estimand attributes are clearly described (population, treatments incl. spacer condition, variables for lung availability vs systemic exposure, and population-level summaries).

The rule to compare the test product with the reference condition associated with the highest systemic exposure (i.e. pMDI with or without spacer) was accepted by CHMP during Scientific Advice, as it represents a conservative approach for the assessment of systemic safety and ensures that any potential increase in exposure with the DPI formulation is evaluated against the "worst-case" exposure scenario of the authorised reference pMDI formulation.

The ICE handling via principal stratum is internally consistent with the objective of comparing exposures under valid dosing/sampling conditions, but it is effectively an exclusion-based strategy and may reduce precision and increase sensitivity to protocol deviations. The Applicant has provided a structured summary of the frequency and reasons for excluded PK parameters by analyte, treatment and period. Exclusions were limited, based on pre-specified rules, and no consistent imbalance across treatments or periods was observed. Therefore, the impact on the comparative PK analyses is considered negligible.

For $AUC_{0-30min}$, the use of the relative actual sampling time as the end time is acceptable and was pre-specified in the SAP. With the response to the RSI, the Applicant has provided a descriptive summary of actual early sampling times by treatment, showing that median and interquartile ranges closely match the planned timepoints and that variability (minimum–maximum) is comparable across

treatments. No systematic differences in sampling times were identified. Therefore, the estimation of $AUC_{0\text{-}30min}$ is not considered to be impacted by sampling time deviations.

Intercurrent events: 'No valid PK measurements'

The SAP lists "no valid PK measurements" among the intercurrent events. However, based on the definitions provided under Section 2.1.2 (Endpoints and derivation rules), situations leading to non-estimable PK parameters (e.g. insufficient terminal data for estimation of λz and AUC_0–inf) primarily reflect limitations of the sampling scheme or data quality rather than intercurrent events in the sense of ICH E9(R1).

The Applicant clarified that this intercurrent event category was intended to capture rare, unforeseeable situations affecting all PK measurements for a subject within a study period (e.g. systematic sample handling or storage issues), and not parameter-specific limitations. No such event occurred in the study and therefore this category had no impact on inclusion or exclusion of PK parameters in the analyses. The handling approach was pre-specified and would have been applied consistently across treatments.

Important protocol deviations and PK data excluded from PK analysis

Important protocol deviations were reported in 8 (12.1%) of the 66 randomised and treated subjects, of whom 6 (9.1%) had deviations reported as leading to the exclusion of PK parameters from the PK set.

Based on the PK results presented, differences in the number of subjects contributing to the analysis of individual PK parameters reflect parameter- and analyte-specific exclusions due to predefined intercurrent events or sampling deviations (e.g. missing or out-of-window late timepoints for glycopyrronium). This pattern is consistent with what would be expected in a parameter-specific pharmacokinetic analysis applying a principal stratum strategy for intercurrent event handling. Subjects were not excluded wholesale from the PK analysis set; rather, specific PK parameters for a given analyte and period were excluded where the underlying concentration–time profile was incomplete for that parameter.

Listing 16.2.5.5 ("PK data excluded from PK analysis") comprises approximately 60 pages. With the response to the RSI, the Applicant has provided a structured summary of PK data exclusions for both primary and secondary PK parameters, including the number of excluded profiles by analyte, parameter, treatment and study period, as well as the reasons for exclusion. For primary PK parameters, exclusions were limited in frequency (generally ≤3%) and related mainly to predefined intercurrent events (e.g. vomiting within the relevant time window) or sampling/data issues (e.g. missing or invalid samples). The distribution of exclusions was comparable across treatment arms and study periods, with no evidence of systematic imbalance.

For secondary PK parameters (AUC_0–inf and t½), a higher number of exclusions was observed, particularly for glycopyrronium bromide, mainly due to predefined PK quality criteria such as high extrapolated fraction (AUC%extrap >20%) and insufficient terminal phase characterisation (R^2adj <0.85). These exclusions are consistent with known methodological limitations and were also similarly distributed across treatments.

Incorrect inhalation manoeuvres were reported in 2 (3.0%) subjects. These events were documented in the eCRF at the time of dosing. In both cases, the incorrect inhalations did not lead to exclusion of PK data from the analysis. The Applicant clarified that these events were prospectively assessed according to predefined protocol deviation criteria distinguishing between important and non-important deviations. Only deviations expected to significantly impact dose delivery or PK interpretability would qualify as intercurrent events leading to exclusion. The reported events were classified as non-

important, as they were not expected to meaningfully affect the delivered dose. This approach is consistent with the SAP-defined handling of incorrect study treatment intake and supports that PK data were retained appropriately.

Selection of the reference condition (R1 vs. R2) at population level

For the assessment of systemic exposure, the statistical analysis refers to a comparison of the test product (T) with the reference condition associated with the highest systemic exposure (R1 or R2). This approach is understood as a conservative, population-level strategy and is consistent with the estimand framework discussed during Scientific Advice.

The Applicant clarified that the reference condition was selected a priori at the population level, for each analyte and PK parameter individually, based on the treatment arm (pMDI with or without spacer) showing the highest systemic exposure. The selected reference was then applied consistently across all subjects and did not vary on a subject-specific basis. For most parameters, pMDI with spacer (R2) was selected, whereas for B17MP AUC_{0-t}, pMDI without spacer (R1) was used.

Results

Lung availability of BDP (T vs. R): Low C_{max} (PE ~49%) with higher AUC_{0-t} (PE ~158%)

For BDP, a markedly lower peak plasma concentration (C_{max}) was observed following administration of the DPI formulation (PE approximately 49%), whereas the extent of exposure (AUC_{0-t}) was substantially higher (PE approximately 158%). This pattern suggests a lower peak but more sustained pulmonary availability with the DPI formulation.

In the context of a line extension involving a different inhaler type, such differences may plausibly be attributed to differences in lung deposition patterns and dissolution characteristics between DPI and pMDI formulations. Importantly, the extent of exposure was not lower with the DPI formulation.

Notably, the request for an additional PK study was primarily driven by limitations of the initial PK study conducted in the COPD development programme, which relied predominantly on the active metabolite B17MP as a surrogate for efficacy. While this approach was considered acceptable in the COPD context, it was deemed insufficient for extrapolation to asthma, where inhaled corticosteroid exposure is more directly linked to local efficacy in the airways.

In the present study CLI-05993BB1-01, these limitations have been adequately addressed. Lung availability was assessed using the parent compound BDP, supported by early and intensive sampling, thereby providing a more direct and specific measure of pulmonary deposition. This approach is scientifically appropriate, as BDP reflects deposition and dissolution in the lung, whereas B17MP represents a composite of pulmonary and systemic conversion and is therefore less specific for local lung exposure.

Overall, the results demonstrate that the extent of BDP exposure (AUC_{0-t}), which reflects the total amount of corticosteroid available at the site of action, is not lower with the DPI formulation compared with the pMDI formulation. Although a lower C_{max} was observed, this is consistent with differences in formulation and inhaler type and does not undermine the assessment of lung availability, particularly given the pharmacology of inhaled corticosteroids. For ICS, sustained exposure rather than peak concentration is considered more relevant for anti-inflammatory efficacy, and dose–response relationships are known to be relatively flat within the approved therapeutic range.

Taken together, the use of BDP as the primary analyte for lung availability, the dense early sampling scheme, and the consistent AUC_{0-t} results provide sufficient reassurance that the DPI formulation delivers an adequate amount of inhaled corticosteroid to the lungs. Therefore, the scientific concerns that motivated the request for a second PK study are considered resolved.

Total systemic exposure of FF (T vs. R with Spacer): Higher AUC_{0-t} (upper limit of 90% CI 136.59%)

For FF, a higher total systemic exposure was observed following administration of the DPI formulation compared with the reference pMDI formulation with spacer. While the point estimate for AUC_{0-t} was below the conventional upper equivalence limit, the upper bound of the 90% confidence interval exceeded the predefined threshold of 125% (upper limit: 136.59%). In contrast, FF C_{max} was comparable between the DPI formulation and the reference pMDI treatment showing the highest exposure.

The applicant attributes the higher AUC_{0-t} primarily to the influence of a single subject with unusually low systemic exposure following reference treatment with spacer, rather than to a consistent increase in FF exposure with the DPI formulation. A post-hoc analysis excluding this subject resulted in an upper confidence limit below the predefined threshold (upper limit of 90% CI 118.27). While this post-hoc analysis is considered supportive only, it may suggest that the observed exceedance is not driven by a systematic formulation-related difference.

From a clinical perspective, the relevance of an increase in total systemic exposure to FF should be interpreted in light of the known pharmacology and safety profile of this LABA component. FF, as part of the dual fixed-dose combination Foster® (BDP/FF), is approved for use at higher cumulative daily doses in asthma, including repeated dosing as maintenance and reliever therapy (MART), with a maximum daily dose of eight inhalations. In contrast, the maximum proposed daily dose of Trimbow® is four inhalations, while each inhalation delivers the same amount of FF as Foster®. Although Trimbow® contains an additional LAMA component contributing to the overall safety profile, the available clinical data for Foster® indicate that higher cumulative daily exposure to FF is generally well tolerated, with manageable cardiovascular effects (see e.g. DE/H/0871/001/II/021).

In addition, interim results from the ongoing TRIBE post-authorisation safety study, designed to further characterise long-term cardiovascular safety of the DPI formulation in a population with higher baseline cardiovascular risk, have not indicated an increased risk of major adverse cardiovascular events compared with the pMDI formulation. Although these data are interim and derived from a COPD population, they provide contextual reassurance regarding the clinical relevance of the higher FF AUC_{0-t} observed in this study.

Overall, while the upper confidence limit for FF AUC_{0-t} exceeded the predefined threshold, the pharmacokinetic and clinical safety data suggest that this finding is of limited clinical relevance and does not indicate a meaningful difference in the systemic safety profile between the DPI and pMDI formulations.

Assessment of AUC_{0-inf} for FF and GB

In addition to the primary analysis based on AUC_{0-t}, the results for AUC_{0-inf} for **FF** warrant further consideration. Although AUC_{0-inf} was not a predefined primary parameter, the observed differences between AUC_0–t and AUC_{0-inf} for FF are notable. In particular, AUC_{0-inf} was evaluable only in a reduced subset of subjects (n=48), and appears to be associated with lower intra-subject variability compared with AUC_{0-t}.

The Applicant clarified that, for the DPI versus pMDI + spacer comparison, FF AUC_{0-inf} was evaluable in 48 subjects. Eighteen subjects were not included: two due to premature discontinuation and 16 due to predefined PK quality criteria or intercurrent event handling rules, mainly AUC%extrap >20%, R^2adj <0.85, or vomiting within 40 minutes post-dose. Exclusions were broadly balanced between DPI and pMDI + spacer (7 and 9 exclusions, respectively), and no systematic treatment-related imbalance was identified.

The mean AUC% extrapolated for formoterol was approximately 12–14% across treatments, supporting that the sampling schedule was generally adequate for terminal phase characterisation in evaluable profiles. $AUC_{0\text{-}inf}$ showed lower intra-subject variability than $AUC_{0\text{-}t}$; however, this appears partly attributable to exclusion of profiles with unreliable terminal phase estimation, including the influential subject with unusually low exposure after pMDI + spacer. Therefore, $AUC_{0\text{-}inf}$ is considered supportive but, due to the reduced and selected analysis subset, is not considered more robust than AUC_0–t for the primary assessment of systemic exposure.

For GB, the Applicant clarified that $AUC_{0\text{-}inf}$ was not reliably estimable in the majority of subjects. Reliable values were available only for 2/65 subjects after DPI, 4/64 after pMDI and 2/65 after pMDI + spacer. Exclusions were mainly driven by predefined PK quality criteria, namely AUC%extrap >20% and insufficient terminal phase fit (R^2adj <0.85). The mean AUC% extrapolated was high across treatments, approximately 36–39%, indicating a substantial contribution of extrapolated exposure.

These data confirm that the terminal elimination phase of GB was not robustly characterised, despite sampling up to 72 hours. Consequently, $AUC_{0\text{-}inf}$ is not considered a reliable endpoint for comparative assessment of GB systemic exposure in this study. However, GB concentrations were generally quantifiable up to the last scheduled sampling time, and $AUC_{0\text{-}t}$ /$AUC_{0\text{–}72h}$ captures observed exposure over an extended sampling interval. Reliance on $AUC_{0\text{-}t}$, together with C_{max}, is therefore considered acceptable for the primary assessment of total systemic exposure under the current study design.

The limited evaluability of GB $AUC_{0\text{-}inf}$ is acknowledged as a methodological limitation, but it does not invalidate the primary systemic exposure comparison based on $AUC_{0\text{-}t}$ and C_{max}.

Comparison between the earlier PK study CCD-05993BA1-01 and the new PK study

In the earlier pharmacokinetic study conducted during the development of the DPI formulation in COPD (CCD-05993BA1-01), differences in systemic exposure for FF and GB were observed with the DPI formulation compared with the pMDI formulation. Specifically, when the DPI (i.e. DPI 2) formulation was compared with pMDI formulation without spacer, substantially higher systemic exposure was reported for FF (C_{max} ratio 161.56; 90% CI 142.88, 182.68; $AUC_{0\text{-}t}$ ratio 122.32; 90% CI 113.43, 131.91) and for GB (C_{max} ratio 223.84; 90% CI 189.04, 265.04). When compared with the pMDI formulation used with spacer, higher systemic exposure was observed only for GB C_{max} (ratio 127.38; 90% CI 105.31, 154.07). These findings raised concerns regarding the systemic exposure profile of the DPI formulation, particularly for GB, and triggered the need for further investigation and post-authorisation safety follow-up (PASS TRIBE).

Direct comparison between the earlier PK study CCD-05993BA1-01 and the new PK study CLI-05993BB1-01 is inherently limited due to differences in study design, including dose level (supratherapeutic versus therapeutic), sampling scheme and reference conditions. In particular, the earlier study relied on different methodological approaches for the assessment of lung availability and systemic exposure (charcoal blockade and non-blockade cohorts) and employed a less intensive early sampling scheme. In contrast, the new PK study was specifically designed to address these limitations, with optimised early blood sampling to allow a more reliable characterisation of early exposure and C_{max} for rapidly absorbed compounds such as FF and GB.

Notwithstanding these methodological differences, the overall exposure patterns observed for FF and GB are similar across both studies. The results of the PK study CLI-05993BB1-01 therefore do not contradict the findings of the earlier study but rather provide a refined and more robust characterisation of systemic exposure under optimised methodological conditions.

2.3.5. Conclusions on clinical pharmacology

Overall, the bioanalytical methods are considered adequately validated and suitable for the intended pharmacokinetic analyses, and the study design is appropriate to support pharmacokinetic bridging between the DPI and pMDI formulations.

The lung availability results demonstrate that exposure to BDP, FF and GB with the DPI formulation is not lower than with the pMDI formulation, thereby supporting comparable efficacy. Although the upper confidence limit for FF AUC_{0-t} exceeded the predefined threshold, peak exposure was comparable and the totality of pharmacokinetic and clinical safety data does not indicate a clinically meaningful increase in systemic exposure. The previously raised concerns regarding systemic exposure to GB observed in the earlier COPD PK study were not confirmed under the optimised methodological conditions of the present study.

The pharmacokinetic data is considered adequate to support the proposed indication extension.

2.4. Clinical efficacy

No clinical efficacy studies in asthma were conducted with the DPI formulation.

2.5. Clinical safety

Introduction

CHF 5993 is a fixed-dose combination of BDP, FF and GB. The safety profile of this triple combination is well established through extensive clinical development programmes and post-marketing experience with the pMDI formulation in both COPD and asthma, as well as with the DPI formulation in COPD.

For the asthma indication, the safety of CHF 5993 pMDI medium and high strength has been characterised in large, long-term Phase III clinical trials (TRIMARAN and TRIGGER), which supported the original approval of the product in adults with inadequately controlled asthma. These studies demonstrated that the addition of the LAMA component to an ICS/LABA backbone did not result in new or unexpected safety signals, including with respect to cardiovascular risk, and that the overall benefit–risk balance was favourable.

The known adverse drug reactions of CHF 5993 are consistent with the established class effects of inhaled corticosteroids, long-acting β2-agonists and long-acting muscarinic antagonists. These include local corticosteroid effects such as oropharyngeal candidiasis and dysphonia, β2-agonist–related effects such as tremor and palpitations, and anticholinergic effects such as dry mouth. Systemic corticosteroid effects are uncommon at recommended doses. Importantly, no increase in asthma-related serious adverse outcomes has been observed when LABA is administered in fixed combination with ICS.

The present application seeks extension of the asthma indication to the CHF 5993 DPI medium strength formulation. No new safety studies in asthma were conducted with the DPI formulation. The updated safety evaluation therefore relies on an integrated assessment of:

- safety data from the CHF 5993 pMDI development programme in asthma (see EMEA/H/C/004257/X/0008/G),
- data from the PK bridging study CLI-05993BB1-01 comparing DPI and pMDI formulations in healthy volunteers, and
- post-marketing safety data, including interim results from an ongoing post-authorisation safety study (PASS) TRIBE in COPD.

Note: This section of the Assessment Report is limited to the evaluation of new clinical safety data submitted in support of the present application. The established safety profile of CHF 5993, as characterised in previous clinical development programmes and post-authorisation assessments for the pressurised metered dose inhaler formulation in asthma and COPD, is not re-assessed in detail in this report and remains unchanged unless explicitly stated.

Patient exposure

New clinical safety data submitted for the present application derive from the single PK study CLI-05993BB1-01 and from post-marketing exposure.

The PK study CLI-05993BB1-01 was a Phase I, randomised, open-label, single-dose, three-way crossover study conducted in healthy adult volunteers. A total of 66 subjects were randomised. Subjects received single therapeutic doses of:

- CHF 5993 DPI medium strength (four inhalations; total dose 400/24/50 µg BDP/FF/GB),
- CHF 5993 pMDI medium strength (four actuations; total dose 400/24/50 µg BDP/FF/GB), and
- CHF 5993 pMDI medium strength administered with a spacer (four actuations; total dose 400/24/50 µg BDP/FF/GB).

Each subject received all three treatments, separated by wash-out periods of at least 21 days.

Post-marketing safety data relate to the use of CHF 5993 DPI medium strength in COPD. Cumulative exposure reported in the most recent periodic safety update report corresponds to approximately 85 million patient-treatment days. Interim data from the ongoing PASS TRIBE study are also available.

Adverse events

Table 16: Summary of Treatment-Emergent Adverse Events (Safety Set)

	CHF5993 100/6/12.5 µg NEXThaler® DPI (T) N=65		CHF5993 100/6/12.5 µg pMDI HFA-134a (R1) N=65		CHF5993 100/6/12.5 µg pMDI HFA-134a With AeroChamber Plus® Spacer (R2) N=65		Overall N=66	
At Least One TEAE	**n (%)**	**E**	**n (%)**	**E**	**n (%)**	**E**	**n (%)**	**E**
TEAE	17 (26.2)	21	12 (18.5)	19	9 (13.8)	13	28 (42.4)	53
Serious TEAE	0		0		0		0	
Non-serious TEAE	17 (26.2)	21	12 (18.5)	19	9 (13.8)	13	28 (42.4)	53
ADR	0		0		1 (1.5)	1	1 (1.5)	1
Serious ADR	0		0		0		0	
Severe TEAE	0		0		0		0	
TEAE leading to study discontinuation	0		0		0		0	
TEAE leading to death	0		0		0		0	

Source: CSP (Version No. 1.0, dated 28 July 2025), Table 26

Table 17: Treatment-Emergent Adverse Events Reported by System Organ Class and Preferred Term (Safety Set)

TEAEs	CHF5993 100/6/12.5 µg NEXThaler® DPI (T) N=65		CHF5993 100/6/12.5 µg pMDI HFA-134a (R1) N=65		CHF5993 100/6/12.5 µg pMDI HFA-134a With AeroChamber Plus® Spacer (R2) N=65		Overall N=66	
	n (%)	E	n (%)	E	n (%)	E	n (%)	E
Any TEAE	*17 (26.2)*	*21*	*12 (18.5)*	*19*	*9 (13.8)*	*13*	*28 (42.4)*	*53*
Nervous System Disorders	**9 (13.8)**	**9**	**5 (7.7)**	**8**	**6 (9.2)**	**7**	**15 (22.7)**	**24**
Headache	8 (12.3)	8	4 (6.2)	6	4 (6.2)	4	11 (16.7)	18
Dizziness	0		1 (1.5)	1	1 (1.5)	1	2 (3.0)	2
Migraine	1 (1.5)	1	0		0		1 (1.5)	1
Neuralgia	0		1 (1.5)	1	0		1 (1.5)	1
Presyncope	0		0		1 (1.5)	1	1 (1.5)	1
Tremor	0		0		1 (1.5)	1	1 (1.5)	1
Infections and Infestations	**5 (7.7)**	**5**	**5 (7.7)**	**5**	**1 (1.5)**	**1**	**10 (15.2)**	**11**
Upper respiratory tract infection	1 (1.5)	1	1 (1.5)	1	1 (1.5)	1	3 (4.5)	3
Cystitis	0		2 (3.1)	2	0		2 (3.0)	2
Nasopharyngitis	1 (1.5)	1	1 (1.5)	1	0		2 (3.0)	2
Bronchitis	1 (1.5)	1	0		0		1 (1.5)	1
Gastroenteritis	1 (1.5)	1	0		0		1 (1.5)	1
Influenza	1 (1.5)	1	0		0		1 (1.5)	1
Pharyngitis	0		1 (1.5)	1	0		1 (1.5)	1
Musculoskeletal and Connective Tissue Disorders	**2 (3.1)**	**2**	**1 (1.5)**	**1**	**3 (4.6)**	**3**	**6 (9.1)**	**6**
Back pain	1 (1.5)	1	0		1 (1.5)	1	2 (3.0)	2
Neck pain	1 (1.5)	1	1 (1.5)	1	0		2 (3.0)	2
Arthralgia	0		0		1 (1.5)	1	1 (1.5)	1
Myalgia	0		0		1 (1.5)	1	1 (1.5)	1
Gastrointestinal Disorders	**3 (4.6)**	**4**	**2 (3.1)**	**2**	**1 (1.5)**	**1**	**5 (7.6)**	**7**
Nausea	1 (1.5)	1	1 (1.5)	1	0		2 (3.0)	2
Vomiting	2 (3.1)	2	0		0		2 (3.0)	2
Abdominal discomfort	0		1 (1.5)	1	0		1 (1.5)	1
Abdominal pain upper	0		0		1 (1.5)	1	1 (1.5)	1
Food poisoning	1 (1.5)	1	0		0		1 (1.5)	1
General Disorders and Administration Site Conditions	**1 (1.5)**	**1**	**2 (3.1)**	**2**	**0**		**3 (4.5)**	**3**
Asthenia	1 (1.5)	1	0		0		1 (1.5)	1
Catheter site haematoma	0		1 (1.5)	1	0		1 (1.5)	1
Exercise tolerance decreased	0		1 (1.5)	1	0		1 (1.5)	1
Respiratory, Thoracic, and Mediastinal Disorders	**0**		**1 (1.5)**	**1**	**1 (1.5)**	**1**	**2 (3.0)**	**2**
Nasal congestion	0		0		1 (1.5)	1	1 (1.5)	1
Oropharyngeal pain	0		1 (1.5)	1	0		1 (1.5)	1

Source: CSP (Version No. 1.0, dated 28 July 2025), Table 27

In the PK study CLI-05993BB1-01, a total of 53 treatment-emergent adverse events (TEAE) were reported in 28 of 66 subjects. Adverse events were reported following all treatments. The majority of events were mild or moderate in intensity. The most frequently reported adverse event was headache.

An increased incidence of headache was observed following administration of the DPI formulation (n=8, 12.3%) compared with the pMDI formulations (n=4, 6.3%). This finding is noted; however, the absolute number of events was small, no severe headaches were reported, and no consistent pattern with respect to dose, timing or associated pharmacokinetic parameters was identified. Given the limited sample size of the study and its single-dose design, the observed difference is considered of uncertain clinical relevance and may reflect random variability.

Other adverse events occurred at low frequency, with each individual event reported in only a single subject.

Overall, no clinically meaningful differences in the type or frequency of adverse events were observed between the DPI formulation and the pMDI formulations, with or without spacer.

One TEAE in one (1.5%) subject was considered to be treatment-related by the Investigator: Subject was reported with the TEAE tremor of mild intensity approximately 15 min after inhalation of CHF5993 100/6/12.5 µg pMDI with the AeroChamber Plus® spacer in treatment period 1. The event was considered resolved after a duration of 46 min.

Serious adverse event/deaths/other significant events

No deaths occurred in the PK study CLI-05993BB1-01. No serious adverse events were reported. No adverse events leading to clinically significant sequelae were observed.

Interim results from the PASS TRIBE study did not report an excess of serious adverse events in patients receiving CHF 5993 DPI compared with those receiving CHF 5993 pMDI. The PASS is ongoing and interim analyses are descriptive in nature.

Laboratory findings

In the PK study CLI-05993BB1-01, no clinically relevant changes in haematology or clinical chemistry parameters were observed following administration of CHF 5993 DPI or comparator treatments. No laboratory-related adverse events were reported.

No new laboratory safety signals were identified from post-marketing surveillance or interim PASS data.

Safety in special populations

The PK study CLI-05993BB1-01 was conducted in healthy adult volunteers. No patients from special populations (e.g. elderly, renal or hepatic impairment) were included.

The PASS TRIBE study includes patients with COPD treated in routine clinical practice. Interim analyses did not identify population-specific safety findings; however, subgroup analyses remain limited at the interim stage.

Safety related to drug-drug interactions and other interactions

No drug–drug interaction assessments were conducted in the PK study CLI-05993BB1-01.

No interaction-related safety signals specific to CHF 5993 DPI were identified in post-marketing safety data or interim PASS TRIBE analyses.

Discontinuation due to adverse events

In the PK study CLI-05993BB1-01, no subjects discontinued the study due to adverse events.

Discontinuations due to adverse events have not been highlighted as a signal in post-marketing surveillance or interim PASS TRIBE data.

Post marketing experience

Post-marketing safety data are available for CHF 5993 DPI medium strength from its authorised use in COPD.

The ongoing PASS TRIBE study is a non-interventional, retrospective, multinational database cohort study designed to assess the incidence of major adverse cardiovascular events (MACE) in patients with COPD newly treated with CHF 5993 DPI compared with CHF 5993 pMDI.

The second interim analysis of TRIBE, covering the period from August 2021 to December 2023, included over 7,000 new users of CHF 5993 DPI and over 54,000 new users of CHF 5993 pMDI. Interim results showed similar or lower incidence rates of MACE with the DPI formulation compared with the pMDI formulation. No new safety signals were identified at the time of the interim analysis. The study is ongoing and final results are pending.

The following scientific discussion is taken from the Final Assessment Report dated 18 September 2025:

"*This is the second Interim Report for study CLI-05993BA1-05, covering the study period from 1 August 2021 to 31 December 2023. Chiesi submitted annual progress reports for the years 2022 and 2023 and an interim report for 2024. Further interim reports are required for the years 2025, 2026 and 2027. The submission of a final study report within 12 months from end of data collection is foreseen.*

In this report, data of accrual, attrition and study population size, duration of exposure, and MACE IRs were evaluated.

Up to DLP there were 16,753 DPI users and 155,447 pMDI users in the source population across the seven selected countries. Of these, 7,030 new users of DPI (42.0%) and 54,308 new users of pMDI (34.9%) were eligible for the study population. The Netherlands had the highest proportion of eligible patients from the source population (DPI cohort: 55.4%; pMDI cohort: 70.7%), while the UK had the lowest proportion for the DPI cohort (33.6%) and Finland for the pMDI cohort (22.3%). Across all countries, the largest decrease in study population size was due to the exclusion criterion of triple therapy use in the 90 days preceding the index date (24.7% [the Netherlands] to 62.2% [the UK] of the patients fulfilling all inclusion criteria in the DPI cohort and 16.5% [the Netherlands] to 70.8% [the UK] of the patients fulfilling all inclusion criteria in the pMDI cohort).

In all countries and study years, the source and study populations of the pMDI cohort were considerably larger than the DPI cohort. Overall, the pMDI cohort had longer exposure times than the DPI cohort across all countries.

For this interim report, all analyses were performed separately for each selected country. Observed patient accrual in source and study populations was reported overall and by study year.

Descriptive statistics were calculated for the observed exposure time in days. Exposure time was defined for each patient as time from the index date (defined as the date of the first prescription for each study drug where all eligibility criteria were fulfilled) until the end of exposure, death, loss to follow-up (applicable for Germany, the Netherlands, and the UK, due to change of health care provider,

i.e. deregistration from the database), emigration (applicable for the Nordic countries only), or end of study period, whichever occurred first.

In this second report, MACE crude IRs were estimated for all selected countries with a study period ranging from a minimum of 13 months in Finland to a maximum of 28 months in Denmark, the Netherlands and Sweden. The occurrence of MACE varied between the study cohorts and countries. Across countries, the MACE crude IRs for the DPI cohort varied from 69.69 per 1,000 patient-years in Finland to 23.85 per 1,000 patient-years in the UK. For the pMDI cohort, the crude IRs ranged from 98.37 per 1,000 patient-years in Finland to 29.20 per 1,000 patient-years in Denmark. A limited number of MACE events was observed in the DPI cohort in certain countries, i.e., the Netherlands reported no MACE events, and Finland recorded fewer than five events. At this interim stage, the IRs should be interpreted with caution given only crude unadjusted estimates were provided.

Based on observed yearly study population counts, the predicted yearly study population accrual and the total study population size by the end of study period were estimated under linear and geometric growth scenarios. The expected power and required sample size to rule out an IRR of 1.5 or greater in the final report were calculated using the predicted study population sizes, observed crude IRs in pMDI cohort, and observed mean exposure times for each study cohort.

Predictions suggest that patient accrual is likely to be sufficient to meet the required sample size for the final report.

The MAH thoroughly discussed the current results and limitations of the study, and no specific risk for study conduct has been identified by the MAH."

2.5.1. Discussion on clinical safety

The present application concerns extension of the asthma indication to the DPI formulation of CHF 5993 at the medium strength already authorised for COPD. The safety discussion therefore focuses on whether new safety concerns arise from the new indication or target population, and whether the newly submitted data modify the established safety profile of the product.

No new clinical safety studies in asthma were conducted with the DPI formulation. New safety data submitted in support of this application comprise:

- a single-dose PK bridging study (CLI-05993BB1-01) in healthy volunteers, and
- post-marketing safety data for CHF 5993 DPI in COPD, including interim results from the ongoing PASS TRIBE study.

The PK study CLI-05993BB1-01 did not identify new safety concerns. No deaths, serious adverse events or clinically relevant findings in laboratory parameters, vital signs or electrocardiograms were observed. The adverse events reported were mild or moderate and consistent with the known pharmacology of the active substances.

Post-marketing experience with CHF 5993 DPI in COPD represents substantial cumulative exposure.

The second interim report of the PASS TRIBE study was already submitted to EMA and assessed by PRAC (PAM procedure number EMA/PAM/0000274884).

Overall, interim analyses from the ongoing PASS TRIBE study have not indicated an increased cardiovascular risk; however, interpretation is limited as only crude, unadjusted incidence rates are currently available.

No new safety concerns specific to the asthma population have been identified from the newly submitted data. There is no indication of a differential safety profile between asthma and COPD that would necessitate additional risk minimisation measures. The known safety profile of CHF 5993 remains driven by class-related risks associated with inhaled corticosteroids, long-acting β2-agonists and long-acting muscarinic antagonists, which are already adequately described in the SmPC.

Based on the new data, no changes to the SmPC safety sections are considered necessary.

The need for additional post-marketing studies has been considered. The ongoing PASS TRIBE study was initiated prior to this application and is already addressing the main safety concern of interest (cardiovascular risk). Completion of this study is considered appropriate as post-authorisation data and does not preclude granting of the requested indication.

2.5.2. Conclusions on clinical safety

No new safety concern has been identified from the newly submitted data in relation to the extension of the asthma indication to CHF 5993 DPI medium strength. The results of the PK study CLI-05993BB1-01 and the available post-marketing data, including interim PASS TRIBE results, are consistent with the known safety profile of the product.

No differences in safety profile between asthma and COPD populations have been identified that would warrant changes to the SmPC or additional risk minimisation measures.

No additional post-authorisation safety studies are required, as the available data do not raise concerns that would preclude granting of the requested indication. The ongoing PASS TRIBE study should be completed as planned and reported in accordance with the agreed pharmacovigilance framework.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 11.1 is acceptable.

The CHMP endorsed the risk management plan version 11.1 with the following content:

Safety concerns

Important Identified risks:	None
Important Potential risks:	Cardio- and cerebrovascular events
Missing information:	None

Pharmacovigilance plan

Study/Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Proposed additional pharmacovigilance activities				
Multinational database cohort study	**Primary Objective:** The primary objective of this study will be to assess the incidence of MACEs, defined as any of the following events: • Myocardial infarction • Stroke (ischemic and haemorrhagic stroke) • Hospitalization due to acute coronary syndrome • Hospitalization due to heart failure **Secondary Objectives:** The secondary objectives of the study will be to assess separately the incidence of each of the following specific events: • Myocardial infarction • Cerebrovascular disorders (ischemic and haemorrhagic stroke, transient ischemic attack) • Hospitalization due to acute coronary syndrome • Hospitalization due to heart failure • Arrhythmias (new-sustained supraventricular and sustained ventricular) • All-cause death	The main aim of the study is to assess adverse cardiovascular and cerebrovascular outcomes in COPD patients which are new users of Trimbow administered via DPI compared to new users of Trimbow administered via pMDI.	**Protocol Approved**	December 2021
			Final report	Within 12-months from End of data collection

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Pharmacovigilance activities
Cardio- and cerebrovascular events	- Statement in section 4.4 and labelled in section 4.8 of the SmPC - Statement in section 2 and in section 4 of the PL	- Routine PhV activities - Additional pharmacovigilance activities: PASS study

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 5.1, 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly. In addition, the Annex IIIA has been revised to amend the QR code links to a video with instructions for use.

No changes to the overall safety profile or contraindications have been introduced beyond those required to reflect the new indication.

2.7.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the MAH show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Asthma is a chronic inflammatory airway disease characterised by variable airflow obstruction, bronchial hyperresponsiveness and respiratory symptoms. In patients with moderate to severe asthma not adequately controlled with ICS and LABA combination therapy, escalation to triple therapy including a LAMA is recommended to reduce exacerbations and improve symptom control.

3.1.2. Available therapies and unmet medical need

Triple therapy with ICS/LABA/LAMA is available for patients whose asthma is not adequately controlled on dual therapy. CHF 5993 pMDI is already authorised for this indication. The current application concerns the extension of indication of Trimbow 88/5/9 mcg to the DPI formulation.

The therapeutic objective is to provide an alternative inhalation device for an already authorised triple fixed-dose combination Trimbow 88/5/9 mcg 88/5/9 mcg, allowing treatment individualisation while maintaining established efficacy and safety.

3.1.3. Main clinical studies

No new Phase III efficacy studies were conducted for the DPI formulation in asthma. The benefit–risk assessment is primarily based on:

- A dedicated pharmacokinetic bridging study (CLI-05993BB1-01) comparing lung availability and systemic exposure of CHF 5993 DPI MS with CHF 5993 pMDI MS (with and without spacer) in healthy volunteers.
- Existing clinical efficacy and safety data for CHF 5993 pMDI in asthma.
- Post-marketing safety data, including interim results from the ongoing PASS TRIBE study.

3.2. Favourable effects

Favourable effects relevant to the present application are derived from pharmacokinetic bridging and established clinical efficacy of the pMDI formulation.

In the PK study CLI-05993BB1-01:

- Lung availability of BDP (assessed by AUC_{0-t}) was not lower with the DPI formulation compared with the pMDI formulation.
- Lung availability of FF and GB (assessed using C_{max} and the early exposure parameter $AUC_{0-30min}$) was not lower with the DPI formulation.
- The use of the parent compound BDP as primary analyte addressed limitations identified in the earlier PK study CCD-05993BA1-01.

Taken together, the PK data demonstrate that the DPI formulation does not deliver lower pulmonary exposure than the authorised pMDI formulation.

As no new efficacy studies were conducted, favourable effects rely on extrapolation from the established clinical efficacy of CHF 5993 pMDI in asthma.

3.3. Uncertainties and limitations about favourable effects

No new clinical efficacy studies were conducted with the DPI formulation in asthma. The demonstration of comparable efficacy is based on pharmacokinetic surrogates of lung availability.

BDP C_{max} was lower with the DPI formulation; however, the clinical relevance of the lower BDP C_{max} is considered limited in view of the non-inferior AUC_{0-t} and the pharmacology of inhaled corticosteroids.

3.4. Unfavourable effects

The safety assessment is based on:

- Systemic exposure data from the PK study CLI-05993BB1-01.
- Established safety profile of CHF 5993 pMDI.
- Post-marketing data including PASS TRIBE.

In the PK study CLI-05993BB1-01:

Systemic exposure to B17MP and GB was not higher with the DPI formulation compared with the pMDI formulation showing the highest exposure.

For FF, AUC_{0-t} showed an upper 90% CI above the predefined threshold (136.59%), while C_{max} was comparable.

Headache was reported more frequently with the DPI formulation; however, the number of events was small, and no clinically relevant pattern was identified.

3.5. Uncertainties and limitations about unfavourable effects

The exceedance of the 125% threshold for formoterol AUC_{0-t} introduces some uncertainty regarding systemic exposure with the DPI formulation.

The PASS TRIBE data are interim and based on crude, unadjusted estimates.

Despite these uncertainties, no clinically meaningful safety signal has been identified. The PASS TRIBE will collect further data on patients' exposure in the post-marketing setting.

3.6. Effects Table

Table 18: Effects Table for Trimbow DPI MS in asthma.

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Lung availability (BDP AUC_{0-t})	Extent of pulmonary exposure not lower with DPI	GMR (%)	DPI	pMDI (R1)	Surrogate marker; based on PK bridging	CLI-05993BB1-01
Lung availability (FF, GB)	Early exposure and C_{max} not lower with DPI	GMR (%)	DPI	pMDI (R1)	Surrogate marker; based on PK bridging	CLI-05993BB1-01
Unfavourable Effects						
FF systemic exposure	Slightly higher AUC_{0-t} (UL 90% CI 136.59%)	GMR (%)	DPI	pMDI (R2)	Upper CI exceeds 125%; post-hoc sensitivity supportive only	CLI-05993BB1-01
Headache	Slightly higher frequency with DPI	n (%)	DPI	pMDI (R2)	Small numbers; limited clinical relevance	CLI-05993BB1-01

Abbreviations: BDP (Beclometasone Dipropionate), B17MP (Beclometasone-17-monopropionate), FF (Formoterol Fumarate), GB (Glycopyrronium Bromide), GMR (Geometric Mean Ratio), CI (Confidence Interval), UL (Upper Limit)

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The primary favourable effect is maintenance of lung availability comparable to the authorised pMDI formulation. The main unfavourable effect requiring consideration is the observed increase in formoterol AUC_{0-t}; however, the pharmacokinetic and clinical safety data suggest that this finding is of limited clinical relevance and does not indicate a meaningful difference in the systemic safety profile between the DPI and pMDI formulations.

3.7.2. Balance of benefits and risks

The benefit–risk assessment relies on pharmacokinetic surrogates rather than new efficacy trials.

The pharmacokinetic bridging study demonstrates that lung availability of the DPI formulation is not lower than that of the authorised pMDI formulation. Systemic exposure findings do not indicate a clinically meaningful increase in safety risk, notwithstanding the exceedance observed for FF AUC_{0-t}.

Overall, pharmacokinetic and clinical safety information does not indicate a meaningful difference in efficacy or safety between the DPI and pMDI formulations.

3.7.3. Additional considerations on the benefit-risk balance

N/A

3.8. Conclusions

The overall B/R of Trimbow 88/5/9 mcg DPI for the maintenance treatment of asthma in adults not adequately controlled with a maintenance combination of a long-acting beta2-agonist and medium dose of inhaled corticosteroid, and who experienced one or more asthma exacerbations in the previous year is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following changes:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Addition of a new therapeutic indication or modification of an approved one	II	I, IIIA, and IIIB

Extension of indication to include treatment of asthma for Trimbow 88/5/9 mcg dry powder inhaler (DPI), based on existing data from the development of Trimbow 87/5/9 mcg pressurised metered dose inhaler (pMDI) in COPD and Asthma, Trimbow 172/5/9 mcg pMDI in Asthma and Trimbow 88/5/9 mcg DPI in COPD, as well as on new data coming from the PK 2 study (CLI-05993BB1-01) and on the interim results of the ongoing PASS (TRIBE) study in COPD. As a consequence, sections 4.1, 4.2, 4.4, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and Labelling are updated in accordance. Version 11.1 of the RMP is approved.

The variation leads to amendments to the annexes I, IIIA, and IIIB and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I, IIIA, and IIIB and to the Risk Management Plan are recommended.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the "EPAR-Procedural steps taken and scientific information after authorisation" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion EMA/VR/0000315173