Summary of Clinical Trial Results

Contents

A. CLINICAL TRIAL INFORMATION

A.1 Trial identifiers and information

Protocol code	CLI-05993AB6-03
Title	A 12-week double-blind, multicentre, randomised, active-controlled, 2-arm, parallel-group clinical trial to evaluate the safety of CHF5993 pMDI 200/6/12.5 µg HFA-152a, compared to CHF5993 pMDI 200/6/12.5 µg HFA-134a, in subjects with asthma.
EU-CT number	2023-503333-22-00
Trial Phase	Therapeutic confirmatory (Phase III)
Medical condition	Moderate to severe controlled asthma
Start of the trial	December 5th, 2023

A.2 Sponsor details

Sponsor organisation name	Chiesi Farmaceutici S.p.A.
Sponsor organisation address	Via Palermo 26/A 43122 Parma – Italy
Scientific and Public contact point	Chiesi Farmaceutici S.p.A., Global Clinical Development clinicaltrials_info@chiesi.com +39 05212791

A.3 Paediatric regulatory details

Not applicable

A.4 Result analysis stage

☐ Intermediate data analysis

☒ Final data analysis

Is this the analysis of the primary completion data?	☒ Yes ☐ No
Additional details, if applicable	Not applicable
Global end of the trial	February 24th, 2025
If applicable, reason for temporary halt or early termination	Not applicable

A.5 General information

Main objective of the trial	The primary objective of this study was to compare the potential for bronchoconstriction with CHF5993 pMDI formulated using the HFA-152a propellant versus CHF5993 pMDI formulated using the HFA-134a propellant, both, at the 200/6/12.5 µg/actuation dosage.
Secondary objectives	The secondary objective of this study was to evaluate the safety and tolerability profile of HFA-152a propellant compared to HFA-134a propellant when administered as CHF5993 200/6/12.5 µg pMDI in adults with moderate to severe controlled asthma.
Trial design	Double-blind, randomised, multicentre, active-controlled, 2-arm parallel-group study
Scientific background and explanation of rationale	The therapeutic indication of the medicinal product used in this study is asthma, a serious and sometimes fatal disease affecting individuals of all ages. An appropriate therapy can significantly reduce exacerbations, one of the major socioeconomic burdens of asthma, and improve patients' quality of life, particularly in those with poorly controlled disease. In this safety study, moderate and severe asthma were defined according to the Global Initiative for Asthma (GINA) 2025 report. As outlined in GINA 2025, asthma treatment follows a stepwise approach, intensifying from low-dose inhaled corticosteroids (ICS) in the early steps to higher ICS doses combined with additional controller therapies such as long-acting β_2-agonists (LABA) and long-acting muscarinic antagonists (LAMA). CHF5993 pressurised metered-dose inhaler (pMDI) solution is a fixed-dose combination of the ICS beclometasone dipropionate

	(BDP), the LABA formoterol fumarate (FF), and the LAMA glycopyrronium bromide (GB). pMDIs are widely used to deliver such treatments, with propellants generating the aerosol cloud. Due to increasing concerns regarding the global warming potential (GWP) of hydrofluorocarbons such as HFA-134a, manufacturers have sought alternative propellants. HFA-152a, a low-GWP propellant with a carbon footprint approximately 90% lower than that of HFA-134a, has emerged as a suitable alternative for pMDI formulations. This clinical pharmacology study was designed to assess the potential for bronchoconstriction and the general safety and tolerability of CHF5993 200/6/12.5 µg pMDI administered as 2 inhalations twice daily (total daily dose, TDD: 800/24/50 µg) via the HFA-152a propellant (test product) and the HFA-134a propellant (reference product) in adult subjects with moderate to severe asthma.
Background Therapy	Not applicable
Measures of protection of trial participants	This trial was conducted in compliance with the protocol, the Declaration of Helsinki (1964 and amendments), current ICH E6 Good Clinical Practices, and all others applicable laws and regulations. The study was authorized by the Health Authorities according to the legal requirements of the country. The selection of participants did not start before the approval by the Ethics Committee was obtained and the study authorized by Health Authorities. Specifically, this trial was conducted in accordance with EU Clinical Trial Regulation 536/2014.
Independent data monitoring committee (IDMC)	Not applicable
Statistical analysis methods used	The following analysis sets were defined for the purposes of the analyses: - *Safety set (SAF)*: all randomised participants who received at least one dose of study treatment (analysed as treated). In case of deviation between as-randomised treatment and treatment received, the treatment received was used in the analyses. - *Per Protocol set (PP)*: all participants from the Safety Set without any important protocol deviations impacting the

	analysis population (e.g., wrong inclusions) leading to the exclusion of the subject from the PP analysis. - *Modified Per Protocol set*: participants from the safety set, without any important protocol deviations related to Asthma Control Questionnaire-6 (ACQ-6) data collected from an unauthorized source (e.g., paper ACQ), which could potentially impact the analysis population (e.g., incorrect inclusions and unverifiable data for analysis), leading to the exclusion of the subject from the Modified PP analysis. The following populations were also defined: – *Enrolled Set*: all participants who provided informed consent (IC) for the study; – *Randomised Set*: all participants randomised to study treatment. For any participant randomised more than once, only the data associated with the first randomised period for which at least one dose of study treatment was received was to be used in any analysis set.

A.6 Population of trial participants

Participants enrolled per Member state concerned (MSC)	**MSC**	**Number**
	Bulgaria	180
	Czech Republic	43
	Germany	142
	Greece	18
	Hungary	39
	Italy	7
	Netherlands	10
	Poland	182
	Romania	48
	Slovakia	29
	Spain	10
	UK	40

Participants enrolled per Countries outside the EEA	Serbia	41
	Georgia	38
Estimated total population for the trial	513	
Participants randomized per age range	☒ 18 – 64 years: 430 participants ☒ 65 – 84 years: 123 participants	
Participants randomised per gender	☒ male: 219 participants ☒ female: 334 participants	
Clinical Trial group	☒ *Patients*	

B. PARTICIPANT DISPOSITION

B.1 Recruitment

Recruitment details	This was a multicentre study conducted in 137 centres located in 14 countries (no participants were recruited in Armenia). In total, 827 participants were enrolled, of whom 553 participants were randomised to one of the two treatment arms: • CHF5993 800/24/50 µg pMDI HFA-152a → 368 participants; • CHF5993 800/24/50 µg pMDI HFA-134a → 185 participants. All 553 randomised participants received at least one dose of study treatment. In total, 14 randomized participants discontinued the study prematurely, of whom 12 had received CHF5993 800/24/50 µg pMDI HFA-152a and 2 had received CHF5993 800/24/50 µg pMDI HFA-134a. The primary reason for study discontinuation was withdrawal of consent (4 participants with CHF5993 800/24/50 µg pMDI HFA-152a and 2 for CHF5993 800/24/50 µg pMDI HFA-134a); additional reasons for study discontinuation reported with CHF5993 800/24/50 µg pMDI HFA-152a included adverse events (AEs) (3 participants), participant permanently discontinued study treatment (2 participants), lost to follow-up (1 participant), participant's medical condition required a change in asthma treatment corresponding to a non-permitted medication (1 participant) and other (1 participant). The reported 'other' reason for study discontinuation was 'the e-diary had a lot of technical issues, and the patient did not want to continue the study'.
Main Inclusion criteria	1. Participant's written informed consent (IC) obtained prior to any study-related procedure;

	2. Males and females, aged ≥18 and ≤75; 3. Body mass index (BMI) within the range of 18.0 to 35.0 kg/m^2 inclusive; 4. Non- or ex-smokers who smoked <10 pack-years (pack-years= number of cigarette packs per day x number of years) and stopped smoking >1 year (6 months for e-cigarettes) prior to screening; 5. Diagnosis of asthma: physician-diagnosed asthma for at least 6 months and with diagnosis before the age of 50 years; 6. Stable asthma therapy with medium/high-dose ICS–LABA ± LAMA (fixed or free combination) for ≥4 weeks prior to screening, as defined by GINA 2022 (BDP non-extrafine >500–1000 µg and >1000 µg, or equivalent). Participants using a spacer with pMDI were required to continue its use throughout the study. 7. Controlled or partly controlled asthma based on an Asthma Control Questionnaire (ACQ)-7 score; 8. Participants with a pre-bronchodilator (BD) forced expiratory volume in the first second (FEV_1) between 40% and 90% of their predicted normal value, after appropriate wash-out from BDs, at the Screening Visit; 9. Participants with a positive BD response at screening defined as an increase in FEV_1 ≥12% and 200 mL over baseline within 30 min after inhalation of 400 µg salbutamol via pMDI; 10. Participants with a cooperative attitude, able to correctly use pMDI inhalers and the e-Diary, literate, capable of performing required study assessments (including acceptable spirometry), and able to understand study-related risks; 11. Female participants fulfilling one of the following criteria: a. Women of non-childbearing potential (WONCBP) defined as physiologically incapable of becoming pregnant. b. Women of childbearing potential (WOCBP) with non-fertile male partners. c. Women of childbearing potential (WOCBP) with fertile male partners; they and/or their partners had to be willing to use a highly effective birth control method from the signature of the IC and until the follow-up visit.
Main Exclusion criteria	1. History of near fatal asthma, hospitalisation for asthma in intensive care unit which in the judgement of the Investigator may place the subject at undue risk, emergency room (ER) access for asthma in the previous 6 months before enrolment; 2. Asthma exacerbation requiring systemic corticosteroids (SCS) or ER admission or hospitalisation within 4 weeks prior to study entry and/or during the run-in period; 3. Non-permanent asthma: exercise-induced, seasonal asthma (as the only asthma-related diagnosis) not requiring daily asthma control medicine; 4. Asthma participants currently treated with chronic SCS, anti-immunoglobulin E, or any other biologic therapy;

	5. Any concomitant respiratory disease interfering with study evaluation or safety assessment, per Investigator and/or Medical Monitor judgement; 6. Participants with a history of lobectomy, pneumonectomy, or other sizable lung volume resection (total volume of lung removed >25%); 7. Participants with lower respiratory tract infection that required use of antibiotics, if unresolved within 4 weeks prior to screening or if occurring during the run-in period; 8. Participants with active cancer or a history of cancer with less than 5 years disease-free survival time (whether there was evidence of local recurrence or metastases). Localised carcinoma was acceptable; 9. Any clinically significant (CS) abnormal 12-lead ECG that in the Investigator's opinion would have affected efficacy or safety evaluations or place the subjects at risk (the average of the three measurements was considered to check the criterion); 10. Contra-indications to investigational medicinal products (IMPs); 11. History of hypersensitivity to any of the study treatments components or a history of other allergy that in the opinion of the Investigator contraindicated the subject's participation; 12. Participants with a medical history or current diagnosis of narrow-angle glaucoma, symptomatic prostatic hypertrophy, urinary retention bladder neck obstruction that, in the opinion of the Investigator, would have prevented use of anticholinergic agents. 13. Participants using SCS medication in the 4 weeks prior to screening (6 weeks prior to randomisation) or slow-release corticosteroids in the 12 weeks before screening (14 weeks prior to randomisation); 14. Intake of non-permitted concomitant medication; 15. Clinical evidence of candidiasis at the oropharyngeal examination at screening or randomisation; 16. Documented coronavirus disease 2019 (COVID-19) diagnosis within the previous 2 weeks, or associated complications/symptoms, which had not resolved within 14 days prior to screening; 17. Participants with a known or suspected history of alcohol and/or substance/drug abuse within 12 months prior to screening; 18. Participation in other investigational trial(s): participants who received any investigational drug within the 30 days (60 days for biologics) or a more appropriate time as determined by the Investigator; For females only: pregnant or lactating women, where pregnancy was defined as the state of a female after conception and until termination of the gestation, confirmed by a positive pregnancy test; 19. Vaccination: subjects having received a vaccination within 2 weeks prior to screening or during the run-in.
Randomisation and blinding	**Randomisation** A pre-established randomisation list was generated. Participants were centrally assigned through an Interactive Response Technology (IRT) system (using the lowest available randomisation number) to

	one of the two treatment arms in a 2:1 ratio for Test Product (CHF5993 800/24/50 µg pMDI HFA-152a) or Reference Product (CHF5993 800/24/50 µg pMDI HFA-134a). If a participant was withdrawn or discontinued from the study, the participant number was not reassigned to another participant.
	Blinding Blinding used: Double blind Roles blinded: Sponsor's clinical team, participants, Investigators, clinical Monitors and staff of the site involved in the management of the study before unblinding of the data, unless in case of emergency.
Investigational Medicinal Product (IMP)	
IMP name	CHF5993 pMDI HFA-152a
Pharmaceutical form and strength	pMDI with HFA-152a propellant – BDP/FF/GB 200/6/12.5 µg per actuation
Route of administration	Inhalation
Authorisation status	Not Authorised for asthma (the use is justified by the study objectives)
Medicinal product role in trial	☒ Test
Investigational Medicinal Product (IMP)	
IMP name	CHF5993 pMDI HFA-134a
Pharmaceutical form and strenght	pMDI with HFA-134a propellant – BDP/FF/GB 200/6/12.5 µg per actuation
Route of administration	Inhalation
Authorisation status	Authorised
Medicinal product role in trial	☒ Comparator
B.2 Pre-assignment	
Screening details	A Pre-screening Visit (V0) was scheduled 2–7 days before the Screening Visit (Week – 2, V1) or could be combined with V1 if study restrictions and wash-out requirements were met. During V0, the study procedures were explained and informed consent was obtained. The Screening Visit (V1) took place two weeks before the start of treatment to assess subject eligibility, deliver training (pMDI use, e-Diary, e-peak flow meter and recognition of asthma exacerbation).

B.3 Treatment Period (overall period)

Run-in period	The Screening Visit was followed by a 2-week run-in period during which subjects took CHF5993 800/24/50 µg pMDI HFA-134a (2 inhalations twice daily).
Randomised treatment	After the 2-week run-in period, a 12-week, double-blind, treatment period on randomised treatment was carried out. On Day 1 eligible participants were randomised to one of two treatment arms (in a 2:1 ratio) for the 12-week treatment period: • **Test Treatment (T):** CHF5993 800/24/50 µg pMDI HFA-152a (2 inhalations twice daily of CHF5993 200/6/12.5 µg pMDI HFA-152a); • **Reference Treatment (R):** CHF5993 800/24/50 µg pMDI HFA-134a (2 inhalations twice daily of CHF5993 200/6/12.5 µg pMDI HFA-134a). In total, 368 participants received CHF5993 800/24/50 µg pMDI HFA-152a (T) and 185 participants CHF5993 800/24/50 µg pMDI HFA-134a (R). The total duration of the study was approximately 16 weeks for any participant completing the study.

Participant disposition per reporting group

Study period	Enrolled	Randomised	Screening Failures
	827	553	274
	Entered	Completed	Discontinued
Treated with test product	368	356	12[1]
Treated with reference product	185	183	2[1]

B.4 Post Assignment Period

A follow-up call (or visit) was performed from 7 to 10 days after last intake of study treatment (also in case of early termination (ET), if the ET visit was performed less than 7 days after the last study treatment intake) to check any new or unresolved AEs, as well as concomitant medications.

[1] Please refer to "Recruitment details" in "B.1 Recruitment" section

C.BASELINE CHARACTERISTICS

C.1 Age (years) – Range: 18-64/65-84 years

	Test Treatment: pMDI HFA-152a	Reference Treatment: pMDI HFA-134a	Overall
Number of participants	368	185	553
Mean	53.7	53.3	53.5
Std Dev	12.9	13.3	13.0
Median	56.0	54.0	55.0
Min, Max	19, 75	18, 74	18, 75

C.2 Gender (n)

Female	223	111	334
Male	145	74	219

C.3 Race (n)

Asian	1	2	3
White	365	181	546
Black or African American	2	1	3
Other	0	1	1

C.4 Height (cm)

Mean	169.9	170.6	170.2
Std Dev	9.4	9.9	9.5
Median	169.0	170.0	169.0
Min, Max	146, 196	151, 195	146, 196

C.5 Weight (kg)			
Mean	79.87	80.50	80.08
Std Dev	14.34	14.16	14.27
Median	80.00	80.00	80.00
Min, Max	48.0, 123.2	47.0, 122.2	47.0, 123.2
C.6 BMI (kg/m2)			
Mean	27.60	27.62	27.61
Std Dev	4.06	4.10	4.07
Median	27.40	27.30	27.40
Min, Max	18.4, 34.9	18.4, 34.9	18.4, 34.9

D. ENDPOINTS

In light of the objectives defined in Section A.5 (General Information section), this study focused on the analysis of the following parameters the following safety parameter was analysed:

- Relative change from pre-dose in Forced Expiratory Volume in 1 Second (FEV_1) at the 10-min post-dose time point on Day 1.

Secondary safety variables completing the evaluation of FEV_1 and the potential for bronchoconstriction of the study treatments were analysed as follows:

- Relative change from pre-dose in FEV_1 at all post-dose time points at each study visit (Day 1, Day 7 and Week 12: 20 min, 30 min, 1 h and 2 h post-dose; Day 7, Week 4 and Week 12: 10 min post-dose);
- Absolute change from pre-dose in FEV_1 at all post-dose time points at each study visit (Day 1, Day 7 and Week 12: 10 min, 20 min, 30 min, 1 h and 2 h post-dose; Week 4: 10 min post-dose);
- Number and percentage of participants with a decrease from pre-dose in FEV_1 at each post-dose time point and at any post-dose time point >15% at each study visit (Day 1, Day 7 and Week 12: 10 min, 20 min, 30 min, 1 h and 2 h post-dose; Week 4: 10 min post-dose);
- Absolute and relative changes from baseline (i.e. pre-dose FEV_1 at Day 1) in pre-dose FEV_1 at all clinical visits;
- Change from pre-dose in FEV_1 area under the curve from time zero to 2 hours ($AUC_{0\text{-}2h}$) normalised by time ($AUC_{0\text{-}2/2h}$) on Day 1, Day 7 and Week 12;
- Change from baseline at each inter-visit period and over the entire treatment period in morning peak expiratory flow (PEF);
- Change from baseline[2] at each inter-visit period and over the entire treatment period in evening PEF;
- Change from baseline at each inter-visit period and over the entire treatment period in the percentage of days without intake of rescue medication;
- Change from baseline at each inter-visit period and over the entire treatment period in the average daily use of rescue medication (number of inhalations/day);
- Change from baseline at each inter-visit period and over the entire treatment period in the average daily symptoms;
- Change from baseline in ACQ-7 at each study visit.

The primary safety variable analysis was conducted on the Safety Set and the PP Set and Modified PP Set (for sensitivity purposes). All analyses for the secondary safety variables considered to complete the evaluation of FEV_1 (above reported) were conducted using the Safety Set and the PP Set as supportive analysis.

However, the analysis results on the PP Set for the secondary safety variables are not reported in this document as they do not differ from those of the same analysis on the Safety Set.

For the change from baseline in ACQ-7 at each study visit, the Modified PP Set was also used for sensitivity purposes.

Important protocol deviations were reported in 92 (25.0%) participants with CHF5993 800/24/50 µg pMDI HFA-152a (T), and in 51 (27.6%) participants with CHF5993 800/24/50 µg pMDI HFA-134a (R).
A total of 12 (3.3%) participants and 13 (7.0%) participants had at least one important protocol deviation leading to participant exclusion from the PP Set with T and R, respectively.
The categories of important protocol deviations leading to participant exclusion from the PP Set included:

[2] Baseline was calculated as the mean of the values collected over the run-in period

- Exclusion criterion met in 6 (1.6%) participants with T and 8 (4.3%) participants with R;
- Assessment source document incomplete/missing in 5 (1.4%) participants with T and 2 (1.1%) participants with R;
- Inclusion criterion not met in 1 (0.3%) participant with T and 2 (1.1%) participants with R;
- Inclusion criterion not verified in 1 (0.5%) participant with R;
- Kit number used not corresponding to the planned one in 1 (0.3%) participant with T.

A total of 39 participants had at least one important protocol deviation leading to participant exclusion from the Modified PP Set (27 and 12 participants with T and R, respectively).

D.1 Primary Endpoint

Title	Relative change from pre-dose in FEV1 at the 10-min post-dose time point on Day 1	
Description	The primary safety variable is defined as the relative change from pre-dose FEV_1 at the 10-minute post-dose timepoint on Day 1. The pre-dose FEV_1 values are the mean of the two pre-dose assessments (i.e., performed 45 min and 15 min before study medication intake at each visit). For each participant, the relative change was derived as: $\left(\frac{\text{FEV1 at 10 min post-dose} - \text{Pre-dose FEV1}}{\text{Pre-dose FEV1}}\right) \text{x } 100$	
Adjusted mean reported as:	95% confidence interval (CI) and p-values	
Endpoints values	Safety Set	Per Protocol (PP) Set

	CHF5993 800/24/50 µg pMDI HFA-152a (T)
	- N° of participants with data / N° of participants with T: 355/367
	- Adjusted mean: 7.294
	  - CI 95% lower limit: 6.353;
	  - CI 95% upper limit: 8.235.
		CHF5993 800/24/50 µg pMDI HFA-152a (T)
		- N° of participants with data / N° of participants with T: 346/355
		- Adjusted mean: 7.298
		  - CI 95% lower limit: 6.339;
		  - CI 95% upper limit: 8.256.

	CHF5993 800/24/50 µg pMDI HFA-134a (R) - N° of participants with data / N° of participants with R: 179/186	**CHF5993 800/24/50 µg pMDI HFA-134a (R)** - N° of participants with data / N° of participants with R: 167/173

	- Adjusted mean: 8.437 - CI 95% lower limit: 7.112; - CI 95% upper limit: 9.762.	- Adjusted mean: 8.417 - CI 95% lower limit: 7.038; - CI 95% upper limit: 9.797.
	P-values: <0.001	

Statistical Analysis Description

Reporting groups	T vs R	
Analysis type and method	Analysis of the primary safety variable (Safety Set/PP set). The primary Safety variable 1 was analysed using an analysis of covariance (ANCOVA) model. Two analytical strategies were considered to address potential intercurrent events (ICEs), with each event assessed individually: 1. Under the principal stratum strategy, the analysis was limited to subjects assumed to have correctly administered study treatment, respected washout requirements, and had no intake of non-permitted respiratory or rescue medications prior to the visit. 2. Under the composite strategy, data collected after potential use of non-permitted respiratory or rescue medications, or after missed spirometry assessments due to bronchoconstriction or safety concerns, were assumed to reflect a relative decrease from pre-dose in FEV_1 greater than 15%, while all prior data were included in the analysis. Participants were handled according to the principal stratum strategy and the composite strategy applied by imputing a 15.01% decrease in FEV_1 after the occurrence of (intercurrent events) ICEs. The adjusted mean relative change from the pre-dose FEV_1 was analysed using an ANCOVA regression model including treatment arm, spacer use at study entry (yes/no) and asthma medication at study entry (ICS+LABA or ICS+LABA+LAMA) as fixed effect and pre-dose FEV1 value as covariate. Adjusted mean relative changes within T vs R and the adjusted mean difference between treatments were estimated together with their 95% confidence intervals and p-values. Equivalence between T vs R was demonstrated if the 95% CI for the adjusted mean difference was fully contained within the predefined equivalence margins of –10% to +10%.	
Values	Safety Set: T vs R	Per Protocol (PP) Set: T vs R
	Adjusted Mean Difference: -1.143 CI 95% lower limit: -2.769 CI 95% upper limit: 0.483	Adjusted Mean Difference: -1.120 CI 95% lower limit: -2.799 CI 95% upper limit: 0.560

	P-value: 0.168	P-value: 0.191

D.2 Secondary Endpoint

D.2.1 First Secondary Endpoint

Title	Relative change from pre-dose in FEV1 at all the post-dose time points at each study visit
Description	This secondary safety variable is defined as the relative change from pre-dose FEV_1 at all the post-dose timepoints at each study visit (Day 1, Day 7 and Week 12: 20 min, 30 min, 1 h and 2 h post-dose; Day 7, Week 4 and Week 12: 10 min post-dose) The pre-dose FEV_1 values are the mean of the two pre-dose assessments (i.e., performed 45 min and 15 min before study medication intake at each visit). For each participant, the relative change was derived as: $$\left(\frac{\text{FEV1 at 10 min post-dose} - \text{Pre-dose FEV1}}{\text{Pre-dose FEV1}}\right) \text{x } 100$$
Adjusted mean reported as:	95% confidence interval (CI) and p-values

Endpoints values – Safety Set		

Day 1 – 20 mins Post-dose	**CHF5993 800/24/50 µg pMDI HFA-152a (T)**
	- N° of participants with data / N° of participants with T: 344/367
	- Adjusted mean: 9.584
	  - CI 95% lower limit: 8.493;
	  - CI 95% upper limit: 10.676.
		CHF5993 800/24/50 µg pMDI HFA-134a (R)
		- N° of participants with data / N° of participants with R: 169/186
		- Adjusted mean: 10.035
		  - CI 95% lower limit: 8.478;
		  - CI 95% upper limit: 11.593.

	P-values: < 0.001	
Day 1 – 30 mins Post-dose	**CHF5993 800/24/50 µg pMDI HFA-152a (T)** - N° of participants with data / N° of participants with T: 361/367 - Adjusted mean: 11.048	**CHF5993 800/24/50 µg pMDI HFA-134a (R)** - N° of participants with data / N° of participants with R: 181/186 - Adjusted mean: 12.090

	- CI 95% lower limit: 9.832; - CI 95% upper limit: 12.264.	- CI 95% lower limit: 10.373; - CI 95% upper limit: 13.808.
	P-values: < 0.001	
Day 1 – 1 Hour Post-dose	**CHF5993 800/24/50 µg pMDI HFA-152a (T)** - N° of participants with data / N° of participants with T: 362/367 - Adjusted mean: 11.476 - CI 95% lower limit: 10.191; - CI 95% upper limit: 12.761.	**CHF5993 800/24/50 µg pMDI HFA-134a (R)** - N° of participants with data / N° of participants with R: 184/186 - Adjusted mean: 12.293 - CI 95% lower limit: 10.490; - CI 95% upper limit: 14.095.
	P-values: < 0.001	
Day 1 – 2 Hours Post-dose	**CHF5993 800/24/50 µg pMDI HFA-152a (T)** - N° of participants with data / N° of participants with T: 363/367 - Adjusted mean: 12.116 - CI 95% lower limit: 10.870; - CI 95% upper limit: 13.361.	**CHF5993 800/24/50 µg pMDI HFA-134a (R)** - N° of participants with data / N° of participants with R: 184/186 - Adjusted mean: 12.969 - CI 95% lower limit: 11.219; - CI 95% upper limit: 14.719.
	P-values: < 0.001	
Day 7 – 10 mins Post-dose	**CHF5993 800/24/50 µg pMDI HFA-152a (T)** - N° of participants with data / N° of participants with T: 355/368 - Adjusted mean: 7.268 - CI 95% lower limit: 6.444; - CI 95% upper limit: 8.092.	**CHF5993 800/24/50 µg pMDI HFA-134a (R)** - N° of participants with data / N° of participants with R: 180/185 - Adjusted mean: 7.947 - CI 95% lower limit: 6.790; - CI 95% upper limit: 9.105.
	P-values: < 0.001	

Day 7 – 20 mins Post-dose	**CHF5993 800/24/50 µg pMDI HFA-152a (T)**
	- N° of participants with data / N° of participants with T: 341/368
	- Adjusted mean: 8.916
	  - CI 95% lower limit: 7.984;
	  - CI 95% upper limit: 9.848.
		CHF5993 800/24/50 µg pMDI HFA-134a (R)
		- N° of participants with data / N° of participants with R: 174/185
		- Adjusted mean: 9.077
		  - CI 95% lower limit: 7.772;
		  - CI 95% upper limit: 10.382.

	P-values: < 0.001	

Day 7 – 30 mins Post-dose	**CHF5993 800/24/50 µg pMDI HFA-152a (T)**
	- N° of participants with data / N° of participants with T: 359/368
	- Adjusted mean: 10.340
	  - CI 95% lower limit: 9.333;
	  - CI 95% upper limit: 11.347.
		CHF5993 800/24/50 µg pMDI HFA-134a (R)
		- N° of participants with data / N° of participants with R: 181/185
		- Adjusted mean: 10.623
		  - CI 95% lower limit: 9.205;
		  - CI 95% upper limit: 12.041.

	P-values: < 0.001	

Day 7 – 1 Hour Post-dose	**CHF5993 800/24/50 µg pMDI HFA-152a (T)**
	- N° of participants with data / N° of participants with T: 361/368
	- Adjusted mean: 10.544
	  - CI 95% lower limit: 9.536;
	  - CI 95% upper limit: 11.551.
		CHF5993 800/24/50 µg pMDI HFA-134a (R)
		- N° of participants with data / N° of participants with R: 184/185
		- Adjusted mean: 10.065
		  - CI 95% lower limit: 8.654;
		  - CI 95% upper limit: 11.477.

	P-values: < 0.001	
Day 7 – 2 Hours Post-dose	**CHF5993 800/24/50 µg pMDI HFA-152a (T)** - N° of participants with data / N° of participants with T: 359/368 - Adjusted mean: 11.110	**CHF5993 800/24/50 µg pMDI HFA-134a (R)** - N° of participants with data / N° of participants with R: 185/185 - Adjusted mean: 11.521

	- CI 95% lower limit: 10.037; - CI 95% upper limit: 12.182.	- CI 95% lower limit: 10.026; - CI 95% upper limit: 13.015.
	P-values: < 0.001	
Week 4 – 10 mins Post-dose	**CHF5993 800/24/50 µg pMDI HFA-152a (T)** - N° of participants with data / N° of participants with T: 341/368 - Adjusted mean: 8.010 - CI 95% lower limit: 7.073; - CI 95% upper limit: 8.947.	**CHF5993 800/24/50 µg pMDI HFA-134a (R)** - N° of participants with data / N° of participants with R: 174/185 - Adjusted mean: 8.006 - CI 95% lower limit: 6.694; - CI 95% upper limit: 9.319.
	P-values: < 0.001	
Week 12 – 10 mins Post-dose	**CHF5993 800/24/50 µg pMDI HFA-152a (T)** - N° of participants with data / N° of participants with T: 344/368 - Adjusted mean: 7.856 - CI 95% lower limit: 7.008; - CI 95% upper limit: 8.704.	**CHF5993 800/24/50 µg pMDI HFA-134a (R)** - N° of participants with data / N° of participants with R: 176/185 - Adjusted mean: 5.755 - CI 95% lower limit: 4.569; - CI 95% upper limit: 6.940.
	P-values: < 0.001	
Week 12 – 20 mins Post-dose	**CHF5993 800/24/50 µg pMDI HFA-152a (T)** - N° of participants with data / N° of participants with T: 326/368 - Adjusted mean: 9.870 - CI 95% lower limit: 8.852; - CI 95% upper limit: 10.887.	**CHF5993 800/24/50 µg pMDI HFA-134a (R)** - N° of participants with data / N° of participants with R: 172/185 - Adjusted mean: 8.482 - CI 95% lower limit: 7.081; - CI 95% upper limit: 9.882.
	P-values: < 0.001	

Week 12 – 30 mins Post-dose	**CHF5993 800/24/50 µg pMDI HFA-152a (T)**
	- N° of participants with data / N° of participants with T: 350/368
	- Adjusted mean: 10.745
	  - CI 95% lower limit: 9.768;
	  - CI 95% upper limit: 11.721.
		CHF5993 800/24/50 µg pMDI HFA-134a (R)
		- N° of participants with data / N° of participants with R: 181/185
		- Adjusted mean: 9.550
		  - CI 95% lower limit: 8.191;
		  - CI 95% upper limit: 10.908.

	P-values: < 0.001	

Week 12 – 1 Hour Post-dose	**CHF5993 800/24/50 µg pMDI HFA-152a (T)**
	- N° of participants with data / N° of participants with T: 353/368
	- Adjusted mean: 10.505
	  - CI 95% lower limit: 9.439;
	  - CI 95% upper limit: 11.571.
		CHF5993 800/24/50 µg pMDI HFA-134a (R)
		- N° of participants with data / N° of participants with R: 180/185
		- Adjusted mean: 9.339
		  - CI 95% lower limit: 7.847;
		  - CI 95% upper limit: 10.832.

	P-values: < 0.001	

Week 12 – 2 Hours Post-dose	**CHF5993 800/24/50 µg pMDI HFA-152a (T)**
	- N° of participants with data / N° of participants with T: 352/368
	- Adjusted mean: 10.660
	  - CI 95% lower limit: 9.564;
	  - CI 95% upper limit: 11.757.
		CHF5993 800/24/50 µg pMDI HFA-134a (R)
		- N° of participants with data / N° of participants with R: 180/185
		- Adjusted mean: 9.712
		  - CI 95% lower limit: 8.178;
		  - CI 95% upper limit: 11.245.

	P-values: < 0.001	
Statistical Analysis Description		
Reporting groups	T vs R	

Analysis type and method	Analysis of the secondary safety variables (Safety Set). The Secondary Safety variable above descripted was analysed similarly to the primary safety variable and applied the same rules for the consideration of ICEs with the principal stratum and composite strategies.	
Values – Safety Set		
T vs R	**Day 1 – 20 mins Post-dose**	Adjusted Mean Difference: -0.451 CI 95% lower limit: -2.353 CI 95% upper limit: 1.451
		P-value: 0.642
	Day 1 – 30 mins Post-dose	Adjusted Mean Difference: -1.042 CI 95% lower limit: -3.147 CI 95% upper limit: 1.063
		P-value: 0.331
	Day 1 – 1 Hour Post-dose	Adjusted Mean Difference: -0.817 CI 95% lower limit: -3.031 CI 95% upper limit: 1.397
		P-value: 0.469
	Day 1 – 2 Hours Post-dose	Adjusted Mean Difference: -0.853 CI 95% lower limit: -3.001 CI 95% upper limit: 1.295
		P-value: 0.436
	Day 7 – 10 mins Post-dose	Adjusted Mean Difference: -0.679 CI 95% lower limit: -2.100 CI 95% upper limit: 0.742
		P-value: 0.348

	Day 7 – 20 mins Post-dose	Adjusted Mean Difference: -0.161 CI 95% lower limit: -1.765 CI 95% upper limit: 1.443
		P-value: 0.844
	Day 7 – 30 mins Post-dose	Adjusted Mean Difference: -0.283 CI 95% lower limit: -2.022 CI 95% upper limit: 1.456
		P-value: 0.750
	Day 7 – 1 Hour Post-dose	Adjusted Mean Difference: 0.478 CI 95% lower limit: -1.256 CI 95% upper limit: 2.213
		P-value: 0.588
	Day 7 – 2 Hours Post-dose	Adjusted Mean Difference: -0.411 CI 95% lower limit: -2.251 CI 95% upper limit: 1.429
		P-value: 0.661
	Week 4 – 10 mins Post-dose	Adjusted Mean Difference: 0.003 CI 95% lower limit: -1.609 CI 95% upper limit: 1.616
		P-value: 0.997
	Week 12 – 10 mins Post-dose	Adjusted Mean Difference: 2.102 CI 95% lower limit: 0.643 CI 95% upper limit: 3.560

		P-value: 0.005
	Week 12 – 20 mins Post-dose	Adjusted Mean Difference: 1.388 CI 95% lower limit: -0.344 CI 95% upper limit: 3.120
		P-value: 0.116
	Week 12 – 30 mins Post-dose	Adjusted Mean Difference: 1.195 CI 95% lower limit: -0.479 CI 95% upper limit: 2.869
		P-value: 0.161
	Week 12 – 1 Hour Post-dose	Adjusted Mean Difference: 1.166 CI 95% lower limit: -0.669 CI 95% upper limit: 3.000
		P-value: 0.213
	Week 12 – 2 Hours Post-dose	Adjusted Mean Difference: 0.949 CI 95% lower limit: -0.937 CI 95% upper limit: 2.835
		P-value: 0.323

D.2.2 Second Secondary Endpoint

Title	Absolute change from pre-dose in FEV_1 at all post-dose time points at each study visit
Description	This secondary safety variable is defined as the absolute change from pre-dose FEV_1 at all the post-dose time points at each study visit (Day 1, Day 7 and Week 12: 10 min, 20 min, 30 min, 1 h and 2 h post-dose; Week 4: 10 min post-dose) The pre-dose FEV_1 values are the mean of the two pre-dose assessments (i.e., performed 45 min and 15 min before study medication intake at each visit).

<table>
<tr><td>Adjusted mean reported as:</td><td colspan="2">95% confidence interval (CI) and p-values</td></tr>
<tr><td colspan="3">Endpoint values – Safety Set</td></tr>
<tr><td rowspan="2">Day 1 – 10 mins Post-dose</td><td>CHF5993 800/24/50 µg pMDI HFA-152a (T)
- N° of participants with data / N° of participants with T: 355/367
- Adjusted mean: 0.160
- CI 95% lower limit: 0.140;
- CI 95% upper limit: 0.180.</td><td>CHF5993 800/24/50 µg pMDI HFA-134a (R)
- N° of participants with data / N° of participants with R: 179/186
- Adjusted mean: 0.177
- CI 95% lower limit: 0.148;
- CI 95% upper limit: 0.205.</td></tr>
<tr><td colspan="2">P-values: < 0.001</td></tr>
<tr><td rowspan="2">Day 1 – 20 mins Post-dose</td><td>CHF5993 800/24/50 µg pMDI HFA-152a (T)
- N° of participants with data / N° of participants with T: 344/367
- Adjusted mean: 0.208
- CI 95% lower limit: 0.185;
- CI 95% upper limit: 0.231.</td><td>CHF5993 800/24/50 µg pMDI HFA-134a (R)
- N° of participants with data / N° of participants with R: 169/186
- Adjusted mean: 0.213
- CI 95% lower limit: 0.180;
- CI 95% upper limit: 0.245.</td></tr>
<tr><td colspan="2">P-values: < 0.001</td></tr>
<tr><td rowspan="2">Day 1 – 30 mins Post-dose</td><td>CHF5993 800/24/50 µg pMDI HFA-152a (T)
- N° of participants with data / N° of participants with T: 361/367
- Adjusted mean: 0.238
- CI 95% lower limit: 0.213;
- CI 95% upper limit: 0.264.</td><td>CHF5993 800/24/50 µg pMDI HFA-134a (R)
- N° of participants with data / N° of participants with R: 181/186
- Adjusted mean: 0.256
- CI 95% lower limit: 0.220;
- CI 95% upper limit: 0.292.</td></tr>
<tr><td colspan="2">P-values: < 0.001</td></tr>
</table>

Day 1 – 1 Hour Post-dose	**CHF5993 800/24/50 µg pMDI HFA-152a (T)**
	- N° of participants with data / N° of participants with T: 362/367
	- Adjusted mean: 0.245
	  - CI 95% lower limit: 0.218;
	  - CI 95% upper limit: 0.272.
		CHF5993 800/24/50 µg pMDI HFA-134a (R)
		- N° of participants with data / N° of participants with R: 184/186
		- Adjusted mean: 0.256
		  - CI 95% lower limit: 0.219;
		  - CI 95% upper limit: 0.294.

	P-values: < 0.001	

Day 1 – 2 Hours Post-dose	**CHF5993 800/24/50 µg pMDI HFA-152a (T)**
	- N° of participants with data / N° of participants with T: 363/367
	- Adjusted mean: 0.256
	  - CI 95% lower limit: 0.230;
	  - CI 95% upper limit: 0.283.
		CHF5993 800/24/50 µg pMDI HFA-134a (R)
		- N° of participants with data / N° of participants with R: 184/186
		- Adjusted mean: 0.270
		  - CI 95% lower limit: 0.233;
		  - CI 95% upper limit: 0.307.

	P-values: < 0.001	

Day 7 – 10 mins Post-dose	**CHF5993 800/24/50 µg pMDI HFA-152a (T)**
	- N° of participants with data / N° of participants with T: 355/368
	- Adjusted mean: 0.163
	  - CI 95% lower limit: 0.144;
	  - CI 95% upper limit: 0.182.
		CHF5993 800/24/50 µg pMDI HFA-134a (R)
		- N° of participants with data / N° of participants with R: 180/185
		- Adjusted mean: 0.167
		  - CI 95% lower limit: 0.141;
		  - CI 95% upper limit: 0.194.

	P-values: < 0.001	
Day 7 – 20 mins Post-dose	**CHF5993 800/24/50 µg pMDI HFA-152a (T)** - N° of participants with data / N° of participants with T: 341/368 - Adjusted mean: 0.196	**CHF5993 800/24/50 µg pMDI HFA-134a (R)** - N° of participants with data / N° of participants with R: 174/185 - Adjusted mean: 0.191

	- CI 95% lower limit: 0.176; - CI 95% upper limit: 0.217.	- CI 95% lower limit: 0.162; - CI 95% upper limit: 0.220.
	P-values: < 0.001	
Day 7 – 30 mins Post-dose	**CHF5993 800/24/50 µg pMDI HFA-152a (T)** - N° of participants with data / N° of participants with T: 359/368 - Adjusted mean: 0.229 - CI 95% lower limit: 0.207; - CI 95% upper limit: 0.251.	**CHF5993 800/24/50 µg pMDI HFA-134a (R)** - N° of participants with data / N° of participants with R: 181/185 - Adjusted mean: 0.224 - CI 95% lower limit: 0.192; - CI 95% upper limit: 0.255.
	P-values: < 0.001	
Day 7 – 1 Hour Post-dose	**CHF5993 800/24/50 µg pMDI HFA-152a (T)** - N° of participants with data / N° of participants with T: 361/368 - Adjusted mean: 0.230 - CI 95% lower limit: 0.208; - CI 95% upper limit: 0.252.	**CHF5993 800/24/50 µg pMDI HFA-134a (R)** - N° of participants with data / N° of participants with R: 184/185 - Adjusted mean: 0.215 - CI 95% lower limit: 0.184; - CI 95% upper limit: 0.246.
	P-values: < 0.001	
Day 7 – 2 Hours Post-dose	**CHF5993 800/24/50 µg pMDI HFA-152a (T)** - N° of participants with data / N° of participants with T: 359/368 - Adjusted mean: 0.241 - CI 95% lower limit: 0.218; - CI 95% upper limit: 0.265.	**CHF5993 800/24/50 µg pMDI HFA-134a (R)** - N° of participants with data / N° of participants with R: 185/185 - Adjusted mean: 0.241 - CI 95% lower limit: 0.209; - CI 95% upper limit: 0.274.
	P-values: < 0.001	

Week 4 – 10 mins Post-dose	**CHF5993 800/24/50 µg pMDI HFA-152a (T)**
	- N° of participants with data / N° of participants with T: 341/368
	- Adjusted mean: 0.176
	  - CI 95% lower limit: 0.155;
	  - CI 95% upper limit: 0.198.
		CHF5993 800/24/50 µg pMDI HFA-134a (R)
		- N° of participants with data / N° of participants with R: 174/185
		- Adjusted mean: 0.175
		  - CI 95% lower limit: 0.145;
		  - CI 95% upper limit: 0.205.

	P-values: < 0.001	

Week 12 – 10 mins Post-dose	**CHF5993 800/24/50 µg pMDI HFA-152a (T)**
	- N° of participants with data / N° of participants with T: 344/368
	- Adjusted mean: 0.170
	  - CI 95% lower limit: 0.151;
	  - CI 95% upper limit: 0.188.
		CHF5993 800/24/50 µg pMDI HFA-134a (R)
		- N° of participants with data / N° of participants with R: 176/185
		- Adjusted mean: 0.122
		  - CI 95% lower limit: 0.096;
		  - CI 95% upper limit: 0.148.

	P-values: < 0.001	

Week 12 – 20 mins Post-dose	**CHF5993 800/24/50 µg pMDI HFA-152a (T)**
	- N° of participants with data / N° of participants with T: 326/368
	- Adjusted mean: 0.210
	  - CI 95% lower limit: 0.188;
	  - CI 95% upper limit: 0.232.
		CHF5993 800/24/50 µg pMDI HFA-134a (R)
		- N° of participants with data / N° of participants with R: 172/185
		- Adjusted mean: 0.179
		  - CI 95% lower limit: 0.149;
		  - CI 95% upper limit: 0.209.

	P-values: < 0.001	
Week 12 – 30 mins Post-dose	**CHF5993 800/24/50 µg pMDI HFA-152a (T)** - N° of participants with data / N° of participants with T: 350/368 - Adjusted mean: 0.230	**CHF5993 800/24/50 µg pMDI HFA-134a (R)** - N° of participants with data / N° of participants with R: 181/185 - Adjusted mean: 0.199

	- CI 95% lower limit: 0.210; - CI 95% upper limit: 0.251.	- CI 95% lower limit: 0.171; - CI 95% upper limit: 0.228.
	P-values: < 0.001	
Week 12 – 1 Hour Post-dose	**CHF5993 800/24/50 µg pMDI HFA-152a (T)** - N° of participants with data / N° of participants with T: 353/368 - Adjusted mean: 0.220 - CI 95% lower limit: 0.197; - CI 95% upper limit: 0.243.	**CHF5993 800/24/50 µg pMDI HFA-134a (R)** - N° of participants with data / N° of participants with R: 180/185 - Adjusted mean: 0.200 - CI 95% lower limit: 0.168; - CI 95% upper limit: 0.232.
	P-values: < 0.001	
Week 12 – 2 Hours Post-dose	**CHF5993 800/24/50 µg pMDI HFA-152a (T)** - N° of participants with data / N° of participants with T: 352/368 - Adjusted mean: 0.225 - CI 95% lower limit: 0.203; - CI 95% upper limit: 0.247.	**CHF5993 800/24/50 µg pMDI HFA-134a (R)** - N° of participants with data / N° of participants with R: 180/185 - Adjusted mean: 0.208 - CI 95% lower limit: 0.177; - CI 95% upper limit: 0.238.
	P-values: < 0.001	

Statistical Analysis Description

Reporting groups	T vs R
Analysis type and method	Analysis of the secondary safety variables (Safety Set). The Secondary Safety variable above descripted was analysed similarly to the primary safety variable and applied the same rules for the consideration of ICEs with the principal stratum and composite strategies.
Values – Safety Set	

T vs R	**Day 1 – 10 mins Post-dose**	Adjusted Mean Difference: -0.017 CI 95% lower limit: -0.052 CI 95% upper limit: 0.018
		P-value: 0.350
	Day 1 – 20 mins Post-dose	Adjusted Mean Difference: -0.004 CI 95% lower limit: -0.045 CI 95% upper limit: 0.036
		P-value: 0.827
	Day 1 – 30 mins Post-dose	Adjusted Mean Difference: -0.018 CI 95% lower limit: -0.062 CI 95% upper limit: 0.027
		P-value: 0.435
	Day 1 – 1 Hour Post-dose	Adjusted Mean Difference: -0.011 CI 95% lower limit: -0.057 CI 95% upper limit: 0.035
		P-value: 0.638
	Day 1 – 2 Hours Post-dose	Adjusted Mean Difference: -0.014 CI 95% lower limit: -0.059 CI 95% upper limit: 0.032
		P-value: 0.553
	Day 7 – 10 mins Post-dose	Adjusted Mean Difference: -0.005

		CI 95% lower limit: -0.037 CI 95% upper limit: 0.028
		P-value: 0.786
	Day 7 – 20 mins Post-dose	Adjusted Mean Difference: 0.005 CI 95% lower limit: -0.030 CI 95% upper limit: 0.041
		P-value: 0.765
	Day 7 – 30 mins Post-dose	Adjusted Mean Difference: 0.005 CI 95% lower limit: -0.033 CI 95% upper limit: 0.044
		P-value: 0.792
	Day 7 – 1 Hour Post-dose	Adjusted Mean Difference: 0.015 CI 95% lower limit: -0.023 CI 95% upper limit: 0.054
		P-value: 0.439
	Day 7 – 2 Hours Post-dose	Adjusted Mean Difference: 0.000 CI 95% lower limit: -0.041 CI 95% upper limit: 0.040
		P-value: 0.986
	Week 4 – 10 mins Post-dose	Adjusted Mean Difference: 0.002 CI 95% lower limit: -0.035 CI 95% upper limit: 0.038

		P-value: 0.930
	Week 12 – 10 mins Post-dose	Adjusted Mean Difference: 0.048 CI 95% lower limit: 0.016 CI 95% upper limit: 0.080
		P-value: 0.003
	Week 12 – 20 mins Post-dose	Adjusted Mean Difference: 0.031 CI 95% lower limit: -0.006 CI 95% upper limit: 0.068
		P-value: 0.098
	Week 12 – 30 mins Post-dose	Adjusted Mean Difference: 0.031 CI 95% lower limit: -0.005 CI 95% upper limit: 0.066
		P-value: 0.087
	Week 12 – 1 Hour Post-dose	Adjusted Mean Difference: 0.020 CI 95% lower limit: -0.020 CI 95% upper limit: 0.059
		P-value: 0.334
	Week 12 – 2 Hours Post-dose	Adjusted Mean Difference: 0.018 CI 95% lower limit: -0.020 CI 95% upper limit: 0.055
		P-value: 0.359

D.2.3 Third Secondary Endpoint		
Title	Number and percentage of participants with a decrease from pre-dose in FEV_1 at each post-dose time point and at any post-dose time point >15% at each study visit	
Description	This secondary safety variable evaluates the number and percentage of participants with a >15% decrease from pre-dose in FEV_1 at each post-dose time point and at any post-dose time point at each study visit (Day 1, Day 7 and Week 12: 10 min, 20 min, 30 min, 1 h and 2 h post-dose; Week 4: 10 min post-dose) The pre-dose FEV1 values are the mean of the two pre-dose assessments (i.e., performed 45 min and 15 min before study medication intake at each visit).	
Analysis type and method	Analysis of the secondary safety variables (Safety Set). This secondary safety variable was analysed based on the analysis of the first secondary safety variable and applied the same rules for the consideration of ICEs with the principal stratum and composite strategies. A decrease from the pre-dose FEV1 at each post-dose time point of >15% was defined as significant - indicative of a potential bronchoconstriction event - while all other changes were defined as non-significant.	
Data are reported as:	Number and percentage of participants with a < -15% or ≥ -15% relative change from pre dose FEV_1	
Endpoints values – Safety Set		

Day 1 – 10 mins Post-dose	**CHF5993 800/24/50 µg pMDI HFA-152a (T)**
	- N° of participants with data / N° of participants with T: 356/368
	  - Relative Change from Pre-dose < -15%: 0;
	  - Relative Change from Pre-dose ≥ -15%: 356 (100%).
		CHF5993 800/24/50 µg pMDI HFA-134a (R)
		- N° of participants with data / N° of participants with R: 178/185
		  - Relative Change from Pre-dose < -15%: 0;
		  - Relative Change from Pre-dose ≥ -15%: 178 (100%).

Day 1 – 20 mins Post-dose	**CHF5993 800/24/50 µg pMDI HFA-152a (T)**
	- N° of participants with data / N° of participants with T: 345/368
	  - Relative Change from Pre-dose < -15%: 1 (0.3%);
	  - Relative Change from Pre-dose ≥ -15%: 344 (99.7%).
		CHF5993 800/24/50 µg pMDI HFA-134a (R)
		- N° of participants with data / N° of participants with R: 168/185
		  - Relative Change from Pre-dose < -15%: 0;
		  - Relative Change from Pre-dose ≥ -15%: 168 (100%).

Day 1 – 30 mins Post-dose	**CHF5993 800/24/50 µg pMDI HFA-152a (T)**
	- N° of participants with data / N° of participants with T: 362/368
	  - Relative Change from Pre-dose < -15%: 1 (0.3%);
	  - Relative Change from Pre-dose ≥ -15%: 361 (99.7 %).
		CHF5993 800/24/50 µg pMDI HFA-134a (R)
		- N° of participants with data / N° of participants with R: 180/185
		  - Relative Change from Pre-dose < -15%: 0;
		  - Relative Change from Pre-dose ≥ -15%: 180 (100%).

Day 1 – 1 Hour Post-dose	**CHF5993 800/24/50 µg pMDI HFA-152a (T)**
	- N° of participants with data / N° of participants with T: 363/368
	  - Relative Change from Pre-dose < -15%: 2 (0.6%);
	  - Relative Change from Pre-dose ≥ -15%: 361 (99.4%).
		CHF5993 800/24/50 µg pMDI HFA-134a (R)
		- N° of participants with data / N° of participants with R: 183/185
		  - Relative Change from Pre-dose < -15%: 0;
		  - Relative Change from Pre-dose ≥ -15%: 183 (100%).

Day 1 – 2 Hours Post-dose	**CHF5993 800/24/50 µg pMDI HFA-152a (T)**
	- N° of participants with data / N° of participants with T: 364/368
	  - Relative Change from Pre-dose < -15%: 1 (0.3%);
	  - Relative Change from Pre-dose ≥ -15%: 363 (99.7%).
		CHF5993 800/24/50 µg pMDI HFA-134a (R)
		- N° of participants with data / N° of participants with R: 183/185
		  - Relative Change from Pre-dose < -15%: 0;
		  - Relative Change from Pre-dose ≥ -15%: 183 (100%).

Day 1 – Any Timepoint	**CHF5993 800/24/50 µg pMDI HFA-152a (T)**
	- N° of participants with data / N° of participants with T: 367/368
	  - Relative Change from Pre-dose < -15%: 2 (0.5%);
	  - Relative Change from Pre-dose ≥ -15%: 365 (99.5%).
		CHF5993 800/24/50 µg pMDI HFA-134a (R)
		- N° of participants with data / N° of participants with R: 183/185
		  - Relative Change from Pre-dose < -15%: 0;
		  - Relative Change from Pre-dose ≥ -15%: 183 (100%).

Day 7 – 10 mins Post-dose	**CHF5993 800/24/50 µg pMDI HFA-152a (T)**
	- N° of participants with data / N° of participants with T: 355/368
	  - Relative Change from Pre-dose < -15%: 1 (0.3%);
	  - Relative Change from Pre-dose ≥ -15%: 354 (99.7%).
		CHF5993 800/24/50 µg pMDI HFA-134a (R)
		- N° of participants with data / N° of participants with R: 180/185
		  - Relative Change from Pre-dose < -15%: 0;
		  - Relative Change from Pre-dose ≥ -15%: 180 (100%).

Day 7 – 20 mins Post-dose	**CHF5993 800/24/50 µg pMDI HFA-152a (T)**
	- N° of participants with data / N° of participants with T: 341/368
	  - Relative Change from Pre-dose < -15%: 0;
	  - Relative Change from Pre-dose ≥ -15%: 341 (100%).
		CHF5993 800/24/50 µg pMDI HFA-134a (R)
		- N° of participants with data / N° of participants with R: 174/185
		  - Relative Change from Pre-dose < -15%: 0;
		  - Relative Change from Pre-dose ≥ -15%: 174 (100%).

Day 7 – 30 mins Post-dose	**CHF5993 800/24/50 µg pMDI HFA-152a (T)**
	- N° of participants with data / N° of participants with T: 359/368
	  - Relative Change from Pre-dose < -15%: 0;
	  - Relative Change from Pre-dose ≥ -15%: 359 (100%).
		CHF5993 800/24/50 µg pMDI HFA-134a (R)
		- N° of participants with data / N° of participants with R: 181/185
		  - Relative Change from Pre-dose < -15%: 0;
		  - Relative Change from Pre-dose ≥ -15%: 181 (100%).

Day 7 – 1 Hour Post-dose	**CHF5993 800/24/50 µg pMDI HFA-152a (T)**
	- N° of participants with data / N° of participants with T: 361/368
	  - Relative Change from Pre-dose < -15%: 0;
	  - Relative Change from Pre-dose ≥ -15%: 361 (100%).
		CHF5993 800/24/50 µg pMDI HFA-134a (R)
		- N° of participants with data / N° of participants with R: 184/185
		  - Relative Change from Pre-dose < -15%: 1 (0.5%);
		  - Relative Change from Pre-dose ≥ -15%: 183 (99.5%).

Day 7 – 2 Hours Post-dose	**CHF5993 800/24/50 µg pMDI HFA-152a (T)**
	- N° of participants with data / N° of participants with T: 359/368
	  - Relative Change from Pre-dose < -15%: 0;
	  - Relative Change from Pre-dose ≥ -15%: 359 (100%).
		CHF5993 800/24/50 µg pMDI HFA-134a (R)
		- N° of participants with data / N° of participants with R: 185/185
		  - Relative Change from Pre-dose < -15%: 0;
		  - Relative Change from Pre-dose ≥ -15%: 185 (100%).

Day 7 – Any Timepoint	**CHF5993 800/24/50 µg pMDI HFA-152a (T)**
	- N° of participants with data / N° of participants with T: 364/368
	  - Relative Change from Pre-dose < -15%: 1 (0.3%);
	  - Relative Change from Pre-dose ≥ -15%: 363 (99.7%).
		CHF5993 800/24/50 µg pMDI HFA-134a (R)
		- N° of participants with data / N° of participants with R: 185/185
		  - Relative Change from Pre-dose < -15%: 1 (0.5%);
		  - Relative Change from Pre-dose ≥ -15%: 184 (99.5%).

Week 4 – 10 mins Post-dose	**CHF5993 800/24/50 µg pMDI HFA-152a (T)**
	- N° of participants with data / N° of participants with T: 341/368
	  - Relative Change from Pre-dose < -15%: 1 (0.3%);
	  - Relative Change from Pre-dose ≥ -15%: 340 (99.7%).
		CHF5993 800/24/50 µg pMDI HFA-134a (R)
		- N° of participants with data / N° of participants with R: 174/185
		  - Relative Change from Pre-dose < -15%: 0;
		  - Relative Change from Pre-dose ≥ -15%: 174 (100%).

Week 4 – Any Timepoint	**CHF5993 800/24/50 µg pMDI HFA-152a (T)**
	- N° of participants with data / N° of participants with T: 341/368
	  - Relative Change from Pre-dose < -15%: 1 (0.3%);
	  - Relative Change from Pre-dose ≥ -15%: 340 (99.7%).
		CHF5993 800/24/50 µg pMDI HFA-134a (R)
		- N° of participants with data / N° of participants with R: 174/185
		  - Relative Change from Pre-dose < -15%: 0;
		  - Relative Change from Pre-dose ≥ -15%: 174 (100%).

Week 12 - 10 mins Post-dose	**CHF5993 800/24/50 µg pMDI HFA-152a (T)**
	- N° of participants with data / N° of participants with T: 344/368
	  - Relative Change from Pre-dose < -15%: 0;
	  - Relative Change from Pre-dose ≥ -15%: 344 (100%).
		CHF5993 800/24/50 µg pMDI HFA-134a (R)
		- N° of participants with data / N° of participants with R: 176/185
		  - Relative Change from Pre-dose < -15%: 2 (1.1%);
		  - Relative Change from Pre-dose ≥ -15%: 174 (98.9%).

Week 12 - 20 mins Post-dose	**CHF5993 800/24/50 µg pMDI HFA-152a (T)**
	- N° of participants with data / N° of participants with T: 326/368
	  - Relative Change from Pre-dose < -15%: 0;
	  - Relative Change from Pre-dose ≥ -15%: 326 (100%).
		CHF5993 800/24/50 µg pMDI HFA-134a (R)
		- N° of participants with data / N° of participants with R: 172/185
		  - Relative Change from Pre-dose < -15%: 0;
		  - Relative Change from Pre-dose ≥ -15%: 172 (100%).

Week 12 - 30 mins Post-dose	**CHF5993 800/24/50 µg pMDI HFA-152a (T)**
	- N° of participants with data / N° of participants with T: 350/368
	  - Relative Change from Pre-dose < -15%: 0;
	  - Relative Change from Pre-dose ≥ -15%: 350 (100%).
		CHF5993 800/24/50 µg pMDI HFA-134a (R)
		- N° of participants with data / N° of participants with R: 181/185
		  - Relative Change from Pre-dose < -15%: 0;
		  - Relative Change from Pre-dose ≥ -15%: 181(100%).

Week 12 – 1 Hour Post-dose	**CHF5993 800/24/50 µg pMDI HFA-152a (T)**
	- N° of participants with data / N° of participants with T: 353/368
	  - Relative Change from Pre-dose < -15%: 2 (0.6%);
	  - Relative Change from Pre-dose ≥ -15%: 351 (99.4%).
		CHF5993 800/24/50 µg pMDI HFA-134a (R)
		- N° of participants with data / N° of participants with R: 180/185
		  - Relative Change from Pre-dose < -15%: 0;
		  - Relative Change from Pre-dose ≥ -15%: 180 (100%).

Week 12 – 2 Hours Post-dose	**CHF5993 800/24/50 µg pMDI HFA-152a (T)**
	- N° of participants with data / N° of participants with T: 352/368
	  - Relative Change from Pre-dose < -15%: 0;
	  - Relative Change from Pre-dose ≥ -15%:352 (100%).
		CHF5993 800/24/50 µg pMDI HFA-134a (R)
		- N° of participants with data / N° of participants with R: 180/185
		  - Relative Change from Pre-dose < -15%: 2 (1.1%);
		  - Relative Change from Pre-dose ≥ -15%: 178 (98.9%).

Week 12 – Any Timepoint	**CHF5993 800/24/50 µg pMDI HFA-152a (T)**
	- N° of participants with data / N° of participants with T: 355/368
	  - Relative Change from Pre-dose < -15%: 2 (0.6%);
	  - Relative Change from Pre-dose ≥ -15%: 353 (99.4%).
		CHF5993 800/24/50 µg pMDI HFA-134a (R)
		- N° of participants with data / N° of participants with R: 181/185
		  - Relative Change from Pre-dose < -15%: 3 (1.7%);
		  - Relative Change from Pre-dose ≥ -15%: 178 (98.3%).

D.2.4 Fourth Secondary Endpoint

Title	Absolute and relative changes from baseline (i.e. pre-dose FEV_1 at Day 1) in pre-dose FEV_1 at all clinical visits
Description	This secondary safety variable evaluates the absolute and relative changes from baseline (i.e. pre-dose FEV_1 at Day 1) in pre-dose FEV_1 at all clinical visits (Day 1, Day 7, Week 4 and Week 12). Pre-dose is defined as the arithmetic mean of the pre-dose FEV1 measurements (at 45 mins and 15 mins pre-dose) collected at each visit.

	Baseline is defined as the arithmetic mean of the pre-dose FEV1 measurements (at 45 mins and 15 mins pre-dose) collected on Day 1. The change from baseline is defined as the value at the visit minus the baseline value: [value at the visit – baseline value)] In particular: • Change from baseline to pre-dose FEV_1 = pre-dose FEV_1 value at Day 7 / Week 4 / Week 12 – baseline value (i.e., pre-dose FEV_1 at Day 1). • Relative change from baseline to pre-dose FEV_1 = (pre-dose FEV_1 value at Day 7 / Week 4 / Week 12 – baseline value)/baseline value.	
Analysis type and method	Analysis of the secondary safety variables (Safety Set). This secondary safety variable was analysed using descriptive statistics.	
Data are reported as:	Arithmetic mean and 95% confidence interval (CI).	
Endpoint values – Safety Set		

Baseline	**CHF5993 800/24/50 µg pMDI HFA-152a (T)**
	
	- N° of participants with data / N° of participants with T: 367/368
	- Mean (Std Dev): 2.269 (0.692)
	  - CI 95% lower limit: 2.198;
	  - CI 95% upper limit: 2.340.
	- Median (Min, Max): 2.165 (0.97, 4.73)
		CHF5993 800/24/50 µg pMDI HFA-134a (R)
		
		- N° of participants with data / N° of participants with R: 184/185
		- Mean (Std Dev): 2.296 (0.756)
		  - CI 95% lower limit: 2.186;
		  - CI 95% upper limit: 2.406.
		- Median (Min, Max): 2.210 (0.90, 4.66)

Day 7 – Pre-dose	**CHF5993 800/24/50 µg pMDI HFA-152a (T)**
	
	- N° of participants with data / N° of participants with T: 364/368
	- Mean (Std Dev): 2.307 (0.691)
	  - CI 95% lower limit: 2.235;
	  - CI 95% upper limit: 2.378.
		CHF5993 800/24/50 µg pMDI HFA-134a (R)
		
		- N° of participants with data / N° of participants with R: 185/185
		- Mean (Std Dev): 2.319 (0.750)
		  - CI 95% lower limit: 2.211;
		  - CI 95% upper limit: 2.428.

	- Median (Min, Max): 2.230 (0.86, 4.59)	- Median (Min, Max): 2.285 (0.94, 4.59)

Change from Baseline to Day 7 – Pre-dose	**CHF5993 800/24/50 µg pMDI HFA-152a (T)**
	- N° of participants with data / N° of participants with T: 363/368
	- Mean (Std Dev): 0.037 (0.214)
	  - CI 95% lower limit: 0.014;
	  - CI 95% upper limit: 0.059.
	- Median (Min, Max): 0.020 (-0.69, 1.13)
		CHF5993 800/24/50 µg pMDI HFA-134a (R)
		- N° of participants with data / N° of participants with R: 184/185
		- Mean (Std Dev): 0.027 (0.226)
		  - CI 95% lower limit: -0.006;
		  - CI 95% upper limit: 0.060.
		- Median (Min, Max): 0.010 (-0.61, 0.90)

Relative Change from Baseline to Day 7 – Pre-dose	**CHF5993 800/24/50 µg pMDI HFA-152a (T)**
	- N° of participants with data / N° of participants with T: 363/368
	- Mean (Std Dev): 2.237 (10.943)
	  - CI 95% lower limit: 1.108;
	  - CI 95% upper limit: 3.367.
	- Median (Min, Max): 0.734 (-30.33, 81.29)
		CHF5993 800/24/50 µg pMDI HFA-134a (R)
		- N° of participants with data / N° of participants with R: 184/185
		- Mean (Std Dev): 1.674 (10.194)
		  - CI 95% lower limit: 0.191;
		  - CI 95% upper limit: 3.157.
		- Median (Min, Max): 0.563 (-25.97, 42.86)

Week 4 – Pre-dose	**CHF5993 800/24/50 µg pMDI HFA-152a (T)**
	- N° of participants with data / N° of participants with T: 360/368
	- Mean (Std Dev): 2.327 (0.703)
	  - CI 95% lower limit: 2.254;
	  - CI 95% upper limit: 2.400.
	- Median (Min, Max): 2.220 (0.82, 4.63)
		CHF5993 800/24/50 µg pMDI HFA-134a (R)
		- N° of participants with data / N° of participants with R: 183/185
		- Mean (Std Dev): 2.339 (0.743)
		  - CI 95% lower limit: 2.230;
		  - CI 95% upper limit: 2.447.
		- Median (Min, Max): 2.285 (0.68, 4.56)

Change from Baseline to Week 4 – Pre-dose	**CHF5993 800/24/50 µg pMDI HFA-152a (T)**
	- N° of participants with data / N° of participants with T: 359/368
	- Mean (Std Dev): 0.057 (0.266)
	  - CI 95% lower limit: 0.029;
	  - CI 95% upper limit: 0.085.
	- Median (Min, Max): 0.035 (-0.62, 1.58)
		CHF5993 800/24/50 µg pMDI HFA-134a (R)
		- N° of participants with data / N° of participants with R: 182/185
		- Mean (Std Dev): 0.045 (0.249)
		  - CI 95% lower limit: 0.008;
		  - CI 95% upper limit: 0.081.
		- Median (Min, Max): 0.035 (-0.78, 0.97)

Relative Change from Baseline to Week 4 – Pre-dose	**CHF5993 800/24/50 µg pMDI HFA-152a (T)**
	- N° of participants with data / N° of participants with T: 359/368
	- Mean (Std Dev): 3.350 (14.830)
	  - CI 95% lower limit: 1.811;
	  - CI 95% upper limit: 4.890.
	  - Median (Min, Max): 1.545 (-30.39, 141.89)
		CHF5993 800/24/50 µg pMDI HFA-134a (R)
		- N° of participants with data / N° of participants with R: 182/185
		- Mean (Std Dev): 2.732 (11.881)
		  - CI 95% lower limit: 0.994;
		  - CI 95% upper limit: 4.470.
		  - Median (Min, Max): 1.452 (-36.18, 60.40)

Week 12 – Pre-dose	**CHF5993 800/24/50 µg pMDI HFA-152a (T)**
	- N° of participants with data / N° of participants with T: 356/368
	- Mean (Std Dev): 2.323 (0.726)
	  - CI 95% lower limit: 2.248;
	  - CI 95% upper limit: 2.399.
	- Median (Min, Max): 2.213 (0.53, 4.69)
		CHF5993 800/24/50 µg pMDI HFA-134a (R)
		- N° of participants with data / N° of participants with R: 181/185
		- Mean (Std Dev): 2.373 (0.780)
		  - CI 95% lower limit: 2.259;
		  - CI 95% upper limit: 2.487.
		- Median (Min, Max): 2.310 (0.85, 4.78)

Change from Baseline to Week 12 – Pre-dose	**CHF5993 800/24/50 µg pMDI HFA-152a (T)**
	- N° of participants with data / N° of participants with T: 355/368
	- Mean (Std Dev): 0.063 (0.290)
	  - CI 95% lower limit: 0.033;
	  - CI 95% upper limit: 0.094.
	- Median (Min, Max): 0.040 (-0.85, 1.66)
		CHF5993 800/24/50 µg pMDI HFA-134a (R)
		- N° of participants with data / N° of participants with R: 180/185
		- Mean (Std Dev): 0.075 (0.264)
		  - CI 95% lower limit: 0.036;
		  - CI 95% upper limit: 0.113.
		- Median (Min, Max): 0.035 (-0.47, 1.01)

Relative Change from Baseline to Week 12 – Pre-dose	**CHF5993 800/24/50 µg pMDI HFA-152a (T)**
	- N° of participants with data / N° of participants with T: 355/368
	- Mean (Std Dev): 3.351 (14.411)
	  - CI 95% lower limit: 1.847;
	  - CI 95% upper limit: 4.855.
	- Median (Min, Max): 1.915 (-52.70, 101.22)
		CHF5993 800/24/50 µg pMDI HFA-134a (R)
		- N° of participants with data / N° of participants with R: 180/185
		- Mean (Std Dev): 3.999 (12.709)
		  - CI 95% lower limit: 2.130;
		  - CI 95% upper limit: 5.869.
		- Median (Min, Max): 1.773 (-21.36, 51.80)

D.2.5 Fifth Secondary Endpoint

Title	Change from pre-dose in FEV_1 area under the curve from time zero to 2 hours ($AUC_{0\text{-}2h}$) normalised by time ($AUC_{0\text{-}2/2h}$) on Day 1, Day 7 and Week 12.
Description	$AUC_{0\text{-}2h}$ (pg.h/mL) is the area under the plasma concentration-time curve from 0 to 2 h post-dose. The $AUC_{0\text{-}2h}$ was calculated using the linear trapezoidal method and normalised to the length of time ($AUC_{0\text{-}2/2h}$), as follows: $$AUC_{0-2/2h} = \frac{1}{t_5 - t_0} \sum_{i=1}^{5} \frac{(t_i - t_{i-1})(d_i + d_{i-1})}{2}$$ Where d_i is the spirometry value (FEV_1) obtained at time t_i; t_i is the actual time (in minutes) for which d_i is measured. For $t_0 = 0$, d_0 is the mean of the two pre-dose values.

Adjusted mean reported as:	95% confidence interval (CI) and p-values	
Endpoints values – Safety set		

Day 1	**CHF5993 800/24/50 µg pMDI HFA-152a (T)**
	- N° of participants with data / N° of participants with T: 355/368
	- Adjusted mean: 0.226
	  - CI 95% lower limit: 0.203;
	  - CI 95% upper limit: 0.249.
		CHF5993 800/24/50 µg pMDI HFA-134a (R)
		- N° of participants with data / N° of participants with R: 178/185
		- Adjusted mean: 0.236
		  - CI 95% lower limit: 0.203;
		  - CI 95% upper limit: 0.268.

	P-values: < 0.001	

Day 7	**CHF5993 800/24/50 µg pMDI HFA-152a (T)**
	- N° of participants with data / N° of participants with T: 353/368
	- Adjusted mean: 0.215
	  - CI 95% lower limit: 0.195;
	  - CI 95% upper limit: 0.236.
		CHF5993 800/24/50 µg pMDI HFA-134a (R)
		- N° of participants with data / N° of participants with R: 180/185
		- Adjusted mean: 0.210
		  - CI 95% lower limit: 0.181;
		  - CI 95% upper limit: 0.238.

	P-values: < 0.001	

Week 12	**CHF5993 800/24/50 µg pMDI HFA-152a (T)**
	- N° of participants with data / N° of participants with T: 344/368
	- Adjusted mean: 0.210
	  - CI 95% lower limit: 0.191;
	  - CI 95% upper limit: 0.229.
		CHF5993 800/24/50 µg pMDI HFA-134a (R)
		- N° of participants with data / N° of participants with R: 176/185
		- Adjusted mean: 0.180
		  - CI 95% lower limit: 0.154;
		  - CI 95% upper limit: 0.207.

	P-values: < 0.001	

Statistical Analysis Description		
Reporting groups	T vs R	
Analysis type and method	Analysis of the secondary safety variables (Safety Set). This secondary safety variable was analysed using descriptive statistics. Principal stratum and composite strategy were also applied in order to consider ICEs as for the previous endpoints.	
Values		
T vs R	**Day 1**	Adjusted Mean Difference: -0.010 CI 95% lower limit: -0.050 CI 95% upper limit: 0.030
		P-value: 0.621
	Day 7	Adjusted Mean Difference: 0.006 CI 95% lower limit: -0.029 CI 95% upper limit: 0.041
		P-value: 0.753
	Week 12	Adjusted Mean Difference: 0.030 CI 95% lower limit: -0.003 CI 95% upper limit: 0.063
		P-value: 0.076

D.2.6 Sixth Secondary Endpoint	
Title	Change from baseline at each inter-visit period and over the entire treatment period in morning Peak Exploratory Flow (PEF)

Description	This endpoint was summarised as the actual pre-dose morning PEF values at baseline, at each inter-visit period and over the entire treatment period and the absolute changes from baseline to each inter-visit period and over the entire treatment period by treatment arm, where: - Inter-visit period: time interval from the morning session of the day after clinic visit to the morning session of the day of next clinic visit (or the date of end of randomised treatment period for last inter-visit period) - Entire treatment period: Time interval from the morning session of the day after the date of start of randomised treatment period to the morning session of the date of end of randomised treatment period of the study.	
Analysis type and method	Analysis of the secondary safety variables (Safety Set). This secondary safety variable was analysed using descriptive statistics. For statistical analysis, the derived morning "Best PEF" was defined as the highest pre-dose PEF value (50–900 L/min) recorded within each morning e-Diary session and was calculated only for morning sessions with at least two acceptable measurements (in the indicated range). Baseline morning PEF was calculated as the average of derived morning "Best PEF" values collected during the run-in period, provided that at least seven valid values were available. The entire treatment period was considered evaluable if at least one inter-visit period was evaluable.	
Data are reported as:	Arithmetic Mean and 95% confidence interval (CI).	
Endpoint values – Safey Set		

Baseline	**CHF5993 800/24/50 µg pMDI HFA-152a (T)**
	- N° of participants with data / N° of participants with T: 349/368
	- Mean (Std Dev): 343.0 (112.4)
	  - CI 95% lower limit: 331.2;
	  - CI 95% upper limit: 354.9.
	- Median (Min, Max): 323.3 (114, 735)
		CHF5993 800/24/50 µg pMDI HFA-134a (R)
		- N° of participants with data / N° of participants with R: 176/185
		- Mean (Std Dev): 343.1 (118.7)
		  - CI 95% lower limit: 325.5;
		  - CI 95% upper limit: 360.8.
		- Median (Min, Max): 327.6 (87, 723)

Day 1 – Day 7	**CHF5993 800/24/50 µg pMDI HFA-152a (T)**	**CHF5993 800/24/50 µg pMDI HFA-134a (R)**

	- N° of participants with data / N° of participants with T: 351/368
	- Mean (Std Dev): 347.9 (116.7)
	  - CI 95% lower limit: 335.6;
	  - CI 95% upper limit: 360.1.
	- Median (Min, Max): 326.1 (91, 756)
		- N° of participants with data / N° of participants with R: 172/185
		- Mean (Std Dev): 345.6 (120.9)
		  - CI 95% lower limit: 327.4;
		  - CI 95% upper limit: 363.8.
		- Median (Min, Max): 331.3 (97, 700)

Change from Baseline to Day 1 – Day 7	**CHF5993 800/24/50 µg pMDI HFA-152a (T)**
	- N° of participants with data / N° of participants with T: 341/368
	- Mean (Std Dev): 3.4 (45.4)
	  - CI 95% lower limit: -1.4;
	  - CI 95% upper limit: 8.3.
	- Median (Min, Max): 2.0 (-158, 433)
		CHF5993 800/24/50 µg pMDI HFA-134a (R)
		- N° of participants with data / N° of participants with R: 168/185
		- Mean (Std Dev): 3.5 (39.5)
		  - CI 95% lower limit: -2.5;
		  - CI 95% upper limit: 9.5.
		- Median (Min, Max): 0.3 (-98, 237)

Day 7 – Week 4	**CHF5993 800/24/50 µg pMDI HFA-152a (T)**
	- N° of participants with data / N° of participants with T: 352/368
	- Mean (Std Dev): 347.4 (118.1)
	  - CI 95% lower limit: 335.0;
	  - CI 95% upper limit: 359.8.
	- Median (Min, Max): 325.8 (102, 737)
		CHF5993 800/24/50 µg pMDI HFA-134a (R)
		- N° of participants with data / N° of participants with R: 175/185
		- Mean (Std Dev): 341.7 (116.6)
		  - CI 95% lower limit: 324.3;
		  - CI 95% upper limit: 359.1.
		- Median (Min, Max): 326.1 (102, 694)

Change from Baseline to Day 7 – Week 4	**CHF5993 800/24/50 µg pMDI HFA-152a (T)**
	- N° of participants with data / N° of participants with T: 339/368
	- Mean (Std Dev): 6.1 (50.2)
	  - CI 95% lower limit: 0.7;
	  - CI 95% upper limit: 11.4.
	- Median (Min, Max): -1.5 (-132, 414)
		CHF5993 800/24/50 µg pMDI HFA-134a (R)
		- N° of participants with data / N° of participants with R: 169/185
		- Mean (Std Dev): -0.1 (43.9)
		  - CI 95% lower limit: -6.8;
		  - CI 95% upper limit: 6.5.
		- Median (Min, Max): -3.1 (-115, 221)

Week 4 – Week 12	**CHF5993 800/24/50 µg pMDI HFA-152a (T)**	**CHF5993 800/24/50 µg pMDI HFA-134a (R)**

	- N° of participants with data / N° of participants with T: 353/368
	- Mean (Std Dev): 342.9 (119.8)
	  - CI 95% lower limit: 330.3;
	  - CI 95% upper limit: 355.4.
	- Median (Min, Max): 321.1 (100, 737)
		- N° of participants with data / N° of participants with R: 175/185
		- Mean (Std Dev): 340.5 (114.8)
		  - CI 95% lower limit: 323.3;
		  - CI 95% upper limit: 357.6.
		- Median (Min, Max): 331.0 (113, 642)

Change from Baseline to Week 4 – Week 12	**CHF5993 800/24/50 µg pMDI HFA-152a (T)**
	- N° of participants with data / N° of participants with T: 338/368
	- Mean (Std Dev): 3.0 (54.0)
	  - CI 95% lower limit: -2.7;
	  - CI 95% upper limit: 8.8.
	- Median (Min, Max): -2.4 (-151, 393)
		CHF5993 800/24/50 µg pMDI HFA-134a (R)
		- N° of participants with data / N° of participants with R: 169/185
		- Mean (Std Dev): -4.2 (44.1)
		  - CI 95% lower limit: -10.9;
		  - CI 95% upper limit: 2.5.
		- Median (Min, Max): -8.5 (-113, 187)

Over 12 Weeks Treatment Period	**CHF5993 800/24/50 µg pMDI HFA-152a (T)**
	- N° of participants with data / N° of participants with T: 363/368
	- Mean (Std Dev): 344.6 (117.7)
	  - CI 95% lower limit: 332.5;
	  - CI 95% upper limit: 356.8.
	- Median (Min, Max): 323.4 (99, 736)
		CHF5993 800/24/50 µg pMDI HFA-134a (R)
		- N° of participants with data / N° of participants with R: 181/185
		- Mean (Std Dev): 339.8 (114.0)
		  - CI 95% lower limit: 323.1;
		  - CI 95% upper limit: 356.5.
		- Median (Min, Max): 325.4 (110, 655)

Change from Baseline to Over 12 Weeks Treatment Period	**CHF5993 800/24/50 µg pMDI HFA-152a (T)**
	- N° of participants with data / N° of participants with T: 348/368
	- Mean (Std Dev): 4.1 (49.8)
	  - CI 95% lower limit: -1.2;
	  - CI 95% upper limit: 9.3.
	- Median (Min, Max): -0.9 (-146, 403)
		CHF5993 800/24/50 µg pMDI HFA-134a (R)
		- N° of participants with data / N° of participants with R: 175/185
		- Mean (Std Dev): -2.4 (40.8)
		  - CI 95% lower limit: -8.5;
		  - CI 95% upper limit: 3.7.
		- Median (Min, Max): -6.2 (-99, 197)

D.2.7 Seventh Secondary Endpoint

Title	Change from baseline at each inter-visit period and over the entire treatment period in evening PEF	
Description	This endpoint was summarised as the actual pre-dose evening PEF values at baseline, at each inter-visit period and over the entire treatment and the absolute changes from baseline to each inter-visit period and over the entire treatment period by treatment arm, where: - Inter-visit period: time interval from the evening session of the day of clinic visit to the evening session of the day before next clinic visit (or the date of end of randomised treatment period for last inter-visit period) - Entire treatment period: Time interval from the evening session of the day of start of randomised treatment period to the evening session of the day before the end of randomised treatment period of the study.	
Analysis type and method	Analysis of the secondary safety variables (Safety Set). This secondary safety variable was analysed using descriptive statistics. For statistical analysis, the derived evening "Best PEF" was defined as the highest evening PEF value (50–900 L/min) recorded within each evening e-Diary session and was calculated only for evening sessions with at least two acceptable measurements (in the indicated range). Baseline evening PEF was calculated as the average of derived evening "Best PEF" values collected during the run-in period, provided that at least seven valid values were available. The entire treatment period was considered evaluable if at least one inter-visit period was evaluable.	
Data are reported as:	Geometric Least Squares (LS) Means and 95% confidence interval (CI).	
Endpoint values – Safety Set		

Baseline	**CHF5993 800/24/50 µg pMDI HFA-152a (T)**
	- N° of participants with data / N° of participants with T: 345/368
	- Mean (Std Dev): 353.6 (110.2)
	  - CI 95% lower limit: 341.9;
	  - CI 95% upper limit: 365.2.
	- Median (Min, Max): 341.8 (90, 710)
		CHF5993 800/24/50 µg pMDI HFA-134a (R)
		- N° of participants with data / N° of participants with R: 174/185
		- Mean (Std Dev): 355.0 (121.4)
		  - CI 95% lower limit: 336.9;
		  - CI 95% upper limit: 373.2.
		- Median (Min, Max): 335.4 (102, 759)

Day 1 – Day 7	**CHF5993 800/24/50 µg pMDI HFA-152a (T)**
	- N° of participants with data / N° of participants with T: 353/368
	- Mean (Std Dev): 361.4 (117.2)
	  - CI 95% lower limit: 349.2;
	  - CI 95% upper limit: 373.7.
	- Median (Min, Max): 343.7 (101, 791)
		CHF5993 800/24/50 µg pMDI HFA-134a (R)
		- N° of participants with data / N° of participants with R: 175/185
		- Mean (Std Dev): 355.2 (121.0)
		  - CI 95% lower limit: 337.2;
		  - CI 95% upper limit: 373.3.
		- Median (Min, Max): 338.0 (110, 717)

Change from Baseline to Day 1 – Day 7	**CHF5993 800/24/50 µg pMDI HFA-152a (T)**
	- N° of participants with data / N° of participants with T: 338/368
	- Mean (Std Dev): 5.6 (44.6)
	  - CI 95% lower limit: 0.8;
	  - CI 95% upper limit: 10.3.
	Median (Min, Max): 2.8 (-134, 486)
		CHF5993 800/24/50 µg pMDI HFA-134a (R)
		- N° of participants with data / N° of participants with R: 168/185
		- Mean (Std Dev): 2.2 (39.7)
		  - CI 95% lower limit: -3.8;
		  - CI 95% upper limit: 8.2.
		Median (Min, Max): -4.5 (-94, 246)

Day 7 – Week 4	**CHF5993 800/24/50 µg pMDI HFA-152a (T)**
	- N° of participants with data / N° of participants with T: 348/368
	- Mean (Std Dev): 360.4 (118.8)
	  - CI 95% lower limit: 347.8;
	  - CI 95% upper limit: 372.9.
	- Median (Min, Max): 337.7 (88, 771)
		CHF5993 800/24/50 µg pMDI HFA-134a (R)
		- N° of participants with data / N° of participants with R: 175/185
		- Mean (Std Dev): 352.5 (118.4)
		  - CI 95% lower limit: 334.8;
		  - CI 95% upper limit: 370.2.
		- Median (Min, Max): 340.0 (123, 688)

Change from Baseline to Day 7 – Week 4	**CHF5993 800/24/50 µg pMDI HFA-152a (T)**
	- N° of participants with data / N° of participants with T: 333/368
	- Mean (Std Dev): 5.8 (49.9)
	  - CI 95% lower limit: 0.4;
	  - CI 95% upper limit: 11.2.
		CHF5993 800/24/50 µg pMDI HFA-134a (R)
		- N° of participants with data / N° of participants with R: 167/185
		- Mean (Std Dev): 0.9 (43.6)
		  - CI 95% lower limit: -5.8;
		  - CI 95% upper limit: 7.5.

	- Median (Min, Max): -0.8 (-115, 467)	- Median (Min, Max): -2.3 (-148, 242)

Week 4 – Week 12	**CHF5993 800/24/50 µg pMDI HFA-152a (T)**
	- N° of participants with data / N° of participants with T: 354/368
	- Mean (Std Dev): 355.7 (120.3)
	  - CI 95% lower limit: 343.1;
	  - CI 95% upper limit: 368.3.
	- Median (Min, Max): 333.9 (99, 772)
		CHF5993 800/24/50 µg pMDI HFA-134a (R)
		- N° of participants with data / N° of participants with R: 174/185
		- Mean (Std Dev): 350.7 (117.0)
		  - CI 95% lower limit: 333.2;
		  - CI 95% upper limit: 368.2.
		- Median (Min, Max): 343.8 (122, 679)

Change from Baseline to Week 4 – Week 12	**CHF5993 800/24/50 µg pMDI HFA-152a (T)**
	- N° of participants with data / N° of participants with T: 335/368
	- Mean (Std Dev): 3.1 (57.9)
	  - CI 95% lower limit: -3.1;
	  - CI 95% upper limit: 9.3.
	- Median (Min, Max): -1.7 (-161, 451)
		CHF5993 800/24/50 µg pMDI HFA-134a (R)
		- N° of participants with data / N° of participants with R: 166/185
		- Mean (Std Dev): -3.8 (48.2)
		  - CI 95% lower limit: -11.2;
		  - CI 95% upper limit: 3.6.
		- Median (Min, Max): -5.1 (-149, 202)

Over 12 Weeks Treatment Period	**CHF5993 800/24/50 µg pMDI HFA-152a (T)**
	- N° of participants with data / N° of participants with T: 364/368
	- Mean (Std Dev): 357.0 (118.1)
	  - CI 95% lower limit: 344.8;
	  - CI 95% upper limit: 369.1.
	- Median (Min, Max): 338.2 (97, 769)
		CHF5993 800/24/50 µg pMDI HFA-134a (R)
		- N° of participants with data / N° of participants with R: 181/185
		- Mean (Std Dev): 352.1 (116.8)
		  - CI 95% lower limit: 334.9;
		  - CI 95% upper limit: 369.2.
		- Median (Min, Max): 343.7 (127, 684)

Change from Baseline to Over 12 Weeks Treatment Period	**CHF5993 800/24/50 µg pMDI HFA-152a (T)**
	- N° of participants with data / N° of participants with T: 345/368
	- Mean (Std Dev): 4.3 (52.7)
	  - CI 95% lower limit: -1.3;
	  - CI 95% upper limit: 9.9.
	- Median (Min, Max): -0.5 (-131, 458)
		CHF5993 800/24/50 µg pMDI HFA-134a (R)
		- N° of participants with data / N° of participants with R: 173/185
		- Mean (Std Dev): -1.4 (43.6)
		  - CI 95% lower limit: -7.9;
		  - CI 95% upper limit: 5.2.
		- Median (Min, Max): -3.9 (-141, 215)

D.2.8 Eighth Secondary Endpoint

Title	Change from baseline at each inter-visit period and over the entire treatment period in the percentage of days without intake of rescue medication.
Description	This secondary safety variable was summarised as the percentage of rescue medication-free days at each inter-visit period and over the entire treatment period (actual value and absolute change from baseline), where: - Inter-visit period: time interval from the evening session of the day of clinic visit to the morning session of the day of next clinic visit (or the date of end of randomised treatment period for last inter-visit period) - Entire treatment period: Time interval from the evening session of the date of start of randomised treatment period to the morning session of the date of end of randomised treatment period of the study. Rescue medication–free days were defined as days with zero rescue medication use, based on e-Diary data. A rescue medication–free day was considered evaluable if either daytime intake (recorded in the evening session) or nighttime intake (recorded in the following morning session) was available.
Analysis type and method	Analysis of the secondary safety variables (Safety Set). This secondary safety variable was analysed using descriptive statistics. The percentage of rescue medication-free days was calculated at baseline, for each inter-visit period and for the entire 12-week treatment period. Baseline Percentage of rescue medication-free days was calculated as the percentage of days with no rescue medication collected during the run-in period. For each inter-visit period, the percentage of rescue medication–free days was calculated as: $\frac{\text{number of days with no rescue medication during the inter} - \text{visit period}}{\text{number of days with available daily use of rescue medication during the inter} - \text{visit period}} x\ 100$

	A minimum of 7 valid days was required for an inter-visit period to be evaluable, except for Day 1–Day 7, where 3 days were sufficient; otherwise, results were set to missing. Percentage of rescue medication-free days over the entire treatment period was calculated analogously, covering the interval from the evening of treatment initiation to the morning of treatment completion. The entire treatment period was considered evaluable if at least one inter-visit period was evaluable.	
Data are reported as:	Arithmetic Means and 95% confidence interval (CI).	
Endpoint values – Safety Set		

Baseline	**CHF5993 800/24/50 µg pMDI HFA-152a (T)**
	
	- N° of participants with data / N° of participants with T: 367/368
	- Mean (Std Dev): 85.86 (24.82)
	  - CI 95% lower limit: 83.31;
	  - CI 95% upper limit: 88.41.
	- Median (Min, Max): 100.00 (0.0, 100.0)
		CHF5993 800/24/50 µg pMDI HFA-134a (R)
		
		- N° of participants with data / N° of participants with R: 185/185
		- Mean (Std Dev): 84.49 (24.49)
		  - CI 95% lower limit: 80.94;
		  - CI 95% upper limit: 88.05.
		- Median (Min, Max): 93.33 (0.0, 100.0)

Day 1 – Day 7	**CHF5993 800/24/50 µg pMDI HFA-152a (T)**
	
	- N° of participants with data / N° of participants with T: 364/368
	- Mean (Std Dev): 90.37 (22.61)
	  - CI 95% lower limit: 88.04;
	  - CI 95% upper limit: 92.70.
	- Median (Min, Max): 100.00 (0.0, 100.0)
		CHF5993 800/24/50 µg pMDI HFA-134a (R)
		
		- N° of participants with data / N° of participants with R: 184/185
		- Mean (Std Dev): 86.77 (26.27)
		  - CI 95% lower limit: 82.95;
		  - CI 95% upper limit: 90.59.
		- Median (Min, Max): 100.00 (0.0, 100.0)

Change from Baseline to Day 1 – Day 7	**CHF5993 800/24/50 µg pMDI HFA-152a (T)**
	- N° of participants with data / N° of participants with T: 363/368
	- Mean (Std Dev): 4.54 (16.63)
	  - CI 95% lower limit: 2.83;
	  - CI 95% upper limit: 6.26.
	- Median (Min, Max): 0.00 (-78.6, 78.6)
		CHF5993 800/24/50 µg pMDI HFA-134a (R)
		- N° of participants with data / N° of participants with R: 184/185
		- Mean (Std Dev): 2.15 (15.95)
		  - CI 95% lower limit: -0.17;
		  - CI 95% upper limit: 4.47.
		- Median (Min, Max): 0.00 (-83.3, 85.7)

Day 7 – Week 4	**CHF5993 800/24/50 µg pMDI HFA-152a (T)**
	- N° of participants with data / N° of participants with T: 361/368
	- Mean (Std Dev): 90.48 (21.36)
	  - CI 95% lower limit: 88.27;
	  - CI 95% upper limit: 92.70.
	- Median (Min, Max): 100.00 (0.0, 100.0)
		CHF5993 800/24/50 µg pMDI HFA-134a (R)
		- N° of participants with data / N° of participants with R: 180/185
		- Mean (Std Dev): 86.46 (25.80)
		  - CI 95% lower limit: 82.67;
		  - CI 95% upper limit: 90.26.
		- Median (Min, Max): 100.00 (0.0, 100.0)

Change from Baseline to Day 7 – Week 4	**CHF5993 800/24/50 µg pMDI HFA-152a (T)**
	- N° of participants with data / N° of participants with T: 360/368
	- Mean (Std Dev): 4.69 (17.92)
	  - CI 95% lower limit: 2.83;
	  - CI 95% upper limit: 6.55.
	- Median (Min, Max): 0.00 (-100.0, 92.3)
		CHF5993 800/24/50 µg pMDI HFA-134a (R)
		- N° of participants with data / N° of participants with R: 180/185
		- Mean (Std Dev): 1.95 (15.91)
		  - CI 95% lower limit: -0.39;
		  - CI 95% upper limit: 4.29.
		- Median (Min, Max): 0.00 (-77.1, 95.2)

Week 4 – Week 12	**CHF5993 800/24/50 µg pMDI HFA-152a (T)**
	- N° of participants with data / N° of participants with T: 358/368
	- Mean (Std Dev): 91.46 (19.97)
	  - CI 95% lower limit: 89.39;
		CHF5993 800/24/50 µg pMDI HFA-134a (R)
		- N° of participants with data / N° of participants with R: 179/185
		- Mean (Std Dev): 87.91 (24.20)
		  - CI 95% lower limit: 84.34;

	- CI 95% upper limit: 93.54. Median (Min, Max): 100.00 (0.0, 100.0)	- CI 95% upper limit: 91.47. - Median (Min, Max): 98.18 (0.0, 100.0)
Change from Baseline to Week 4 – Week 12	**CHF5993 800/24/50 µg pMDI HFA-152a (T)** - N° of participants with data / N° of participants with T: 357/368 - Mean (Std Dev): 5.43 (19.38) - CI 95% lower limit: 3.41; - CI 95% upper limit: 7.45. - Median (Min, Max): 0.00 (-97.6, 96.4)	**CHF5993 800/24/50 µg pMDI HFA-134a (R)** - N° of participants with data / N° of participants with R: 179/185 - Mean (Std Dev): 3.20 (16.09) - CI 95% lower limit: 0.83; - CI 95% upper limit: 5.58. - Median (Min, Max): 0.00 (-66.7, 73.2)
Over 12 Weeks Treatment Period	**CHF5993 800/24/50 µg pMDI HFA-152a (T)** - N° of participants with data / N° of participants with T: 368/368 - Mean (Std Dev): 90.89 (20.19) - CI 95% lower limit: 88.82; - CI 95% upper limit: 92.95. - Median (Min, Max): 98.81 (0.0, 100.0)	**CHF5993 800/24/50 µg pMDI HFA-134a (R)** - N° of participants with data / N° of participants with R: 185/185 - Mean (Std Dev): 87.71 (23.75) - CI 95% lower limit: 84.26; - CI 95% upper limit: 91.15. - Median (Min, Max): 97.62 (0.0, 100.0)
Change from Baseline to Over 12 Weeks Treatment Period	**CHF5993 800/24/50 µg pMDI HFA-152a (T)** - N° of participants with data / N° of participants with T: 367/368 - Mean (Std Dev): 5.00 (18.14) - CI 95% lower limit: 3.14; - CI 95% upper limit: 6.87. - Median (Min, Max): 0.00 (-98.1, 90.5)	**CHF5993 800/24/50 µg pMDI HFA-134a (R)** - N° of participants with data / N° of participants with R: 185/185 - Mean (Std Dev): 3.21 (15.70) - CI 95% lower limit: 0.93; - CI 95% upper limit: 5.49. - Median (Min, Max): 0.00 (-61.7, 92.9)

D.2.9 Nineth Secondary Endpoint

Title	Change from baseline at each inter-visit period and over the entire treatment period in the average daily use of rescue medication (number of inhalations/day)
Description	This secondary safety variable was summarised as use of rescue medication at least once, average daily use of rescue medication (number of inhalations/day) at each inter-visit period and over the entire treatment period (actual value and absolute change from baseline). Refer to the previous paragraph (D.2.10) for the inter-visit period and entire treatment period definitions.
Analysis type and method	Analysis of the secondary safety variables (Safety Set). This secondary safety variable was analysed using descriptive statistics. Daily rescue medication use was derived from twice-daily (morning and evening) e-Diary entries and calculated as the sum of the number of puffs of rescue medication taken during the daytime (i.e. recorded in the evening e-Diary session of that day) and the number of puffs taken during the nighttime (recorded in the morning e-Diary session of the next day). If one session was missing (morning or evening), the available session was used. Baseline average use of rescue medication was calculated as the mean daily use from the evening e-Diary session of the Screening Visit [Week -2] to the morning e-Diary session of Day 1 (inclusive). For each inter-visit period, average use of rescue medication at each inter-visit period was calculated as the mean of all daily use of rescue medication values recorded in each inter-visit period. A minimum of 7 valid days was required for baseline and for each inter-visit period to be evaluable, except for Day 1–Day 7, where 3 days were sufficient; otherwise, results were set to missing. The entire treatment period was considered evaluable if at least one inter-visit period was evaluable. Only e-Diary data were included in the analysis.
Data are reported as:	Arithmetic Means and 95% confidence interval (CI).

Endpoint values – Safety		
Baseline	**CHF5993 800/24/50 µg pMDI HFA-152a (T)** - N° of participants with data / N° of participants with T: 367/368	**CHF5993 800/24/50 µg pMDI HFA-134a (R)** - N° of participants with data / N° of participants with R: 185/185

	- Mean (Std Dev): 0.309 (0.625)
	  - CI 95% lower limit: 0.244;
	  - CI 95% upper limit: 0.373.
	- Median (Min, Max): 0.000 (0.00, 4.07)
		- Mean (Std Dev): 0.335 (0.632)
		  - CI 95% lower limit: 0.244;
		  - CI 95% upper limit: 0.427.
		- Median (Min, Max): 0.077 (0.00, 4.00)

Day 1 – Day 7	**CHF5993 800/24/50 µg pMDI HFA-152a (T)**
	- N° of participants with data / N° of participants with T: 364/368
	- Mean (Std Dev): 0.243 (0.813)
	  - CI 95% lower limit: 0.160;
	  - CI 95% upper limit: 0.327.
	- Median (Min, Max): 0.000 (0.00, 10.50)
		CHF5993 800/24/50 µg pMDI HFA-134a (R)
		- N° of participants with data / N° of participants with R: 184/185
		- Mean (Std Dev): 0.313 (0.735)
		  - CI 95% lower limit: 0.206;
		  - CI 95% upper limit: 0.420.
		- Median (Min, Max): 0.000 (0.00, 4.00)

Change from Baseline to Day 1 – Day 7	**CHF5993 800/24/50 µg pMDI HFA-152a (T)**
	- N° of participants with data / N° of participants with T: 363/368
	- Mean (Std Dev): -0.066 (0.675)
	  - CI 95% lower limit: -0.135;
	  - CI 95% upper limit: 0.004.
	- Median (Min, Max): 0.000 (-2.57, 8.83)
		CHF5993 800/24/50 µg pMDI HFA-134a (R)
		- N° of participants with data / N° of participants with R: 184/185
		- Mean (Std Dev): -0.021 (0.523)
		  - CI 95% lower limit: -0.097;
		  - CI 95% upper limit: 0.055.
		- Median (Min, Max): 0.000 (-3.71, 3.00)

Day 7 – Week 4	**CHF5993 800/24/50 µg pMDI HFA-152a (T)**
	- N° of participants with data / N° of participants with T: 361/368
	- Mean (Std Dev): 0.233 (0.631)
	  - CI 95% lower limit: 0.168;
	  - CI 95% upper limit: 0.299.
	- Median (Min, Max): 0.000 (0.00, 4.00)
		CHF5993 800/24/50 µg pMDI HFA-134a (R)
		- N° of participants with data / N° of participants with R: 180/185
		- Mean (Std Dev): 0.337 (0.778)
		  - CI 95% lower limit: 0.222;
		  - CI 95% upper limit: 0.451.
		- Median (Min, Max): 0.000 (0.00, 4.00)

Change from Baseline to Day 7 – Week 4	**CHF5993 800/24/50 µg pMDI HFA-152a (T)**
	- N° of participants with data / N° of participants with T: 360/368
	- Mean (Std Dev): -0.075 (0.529)
	  - CI 95% lower limit: -0.130;
	  - CI 95% upper limit: -0.021.
	- Median (Min, Max): 0.000 (-2.83, 3.50)
		CHF5993 800/24/50 µg pMDI HFA-134a (R)
		- N° of participants with data / N° of participants with R: 180/185
		- Mean (Std Dev): 0.001 (0.529)
		  - CI 95% lower limit: -0.077;
		  - CI 95% upper limit: 0.079.
		- Median (Min, Max): 0.000 (-3.90, 3.00)

Week 4 – Week 12	**CHF5993 800/24/50 µg pMDI HFA-152a (T)**
	- N° of participants with data / N° of participants with T: 358/368
	- Mean (Std Dev): 0.203 (0.518)
	  - CI 95% lower limit: 0.149;
	  - CI 95% upper limit: 0.257.
	- Median (Min, Max): 0.000 (0.00, 3.85)
		CHF5993 800/24/50 µg pMDI HFA-134a (R)
		- N° of participants with data / N° of participants with R: 179/185
		- Mean (Std Dev): 0.330 (0.841)
		  - CI 95% lower limit: 0.206;
		  - CI 95% upper limit: 0.454.
		- Median (Min, Max): 0.036 (0.00, 5.35)

Change from Baseline to Week 4 – Week 12	**CHF5993 800/24/50 µg pMDI HFA-152a (T)**
	- N° of participants with data / N° of participants with T: 357/368
	- Mean (Std Dev): -0.101 (0.530)
	  - CI 95% lower limit: -0.156;
	  - CI 95% upper limit: -0.046.
	- Median (Min, Max): 0.000 (-2.83, 3.35)
		CHF5993 800/24/50 µg pMDI HFA-134a (R)
		- N° of participants with data / N° of participants with R: 179/185
		- Mean (Std Dev): 0.009 (0.528)
		  - CI 95% lower limit: -0.069;
		  - CI 95% upper limit: 0.086.
		- Median (Min, Max): 0.000 (-1.46, 3.19)

Over 12 Weeks Treatment Period	**CHF5993 800/24/50 µg pMDI HFA-152a (T)** - N° of participants with data / N° of participants with T: 368/368	**CHF5993 800/24/50 µg pMDI HFA-134a (R)** - N° of participants with data / N° of participants with R: 185/185

	- Mean (Std Dev): 0.238 (0.753) - CI 95% lower limit: 0.161; - CI 95% upper limit: 0.316. Median (Min, Max): 0.024 (0.00, 10.50)	- Mean (Std Dev): 0.323 (0.787) - CI 95% lower limit: 0.209; - CI 95% upper limit: 0.437. - Median (Min, Max): 0.048 (0.00, 4.43)
Change from Baseline to Over 12 Weeks Treatment Period	**CHF5993 800/24/50 µg pMDI HFA-152a (T)** - N° of participants with data / N° of participants with T: 367/368 - Mean (Std Dev): -0.069 (0.684) - CI 95% lower limit: -0.140; - CI 95% upper limit: 0.001. - Median (Min, Max): 0.000 (-2.81, 8.83)	**CHF5993 800/24/50 µg pMDI HFA-134a (R)** - N° of participants with data / N° of participants with R: 185/185 - Mean (Std Dev): -0.012 (0.542) - CI 95% lower limit: -0.091; - CI 95% upper limit: 0.066. - Median (Min, Max): 0.000 (-3.86, 2.98)

D.2.10 Tenth Secondary Endpoint

Title	Change from baseline at each inter-visit period and over the entire treatment period in the average daily asthma symptoms
Description	This secondary safety variable was summarised as the average daily symptoms score at each inter-visit period and over the entire treatment period (actual value and absolute change from baseline). Refer to the previous paragraph (D.2.10) for the inter-visit period and entire treatment period definitions.
Analysis type and method	Analysis of the secondary safety variables (Safety Set). This secondary safety variable was analysed using descriptive statistics. Baseline asthma symptom score was defined as the mean daily symptom score recorded from the evening e-Diary session of Visit 1 to the morning e-Diary session of Day 1. Symptoms to be considered were cough, wheeze, chest tightness, and breathlessness. Daily symptom scores were calculated as the mean of the 8 scores (i.e., cough, wheeze, chest tightness, and breathlessness) recorded in the evening and the following morning e-Diary session; if one session was missing, the available session was used. Baseline was set to missing if fewer than 7 daily entries were available in the run-in period.

	Average total daily asthma symptom scores were calculated as the mean of daily scores within each inter-visit period and over the entire treatment period. A minimum of 7 valid days was required for each inter-visit period to be evaluable, except for Day 1–Day 7, where 3 days were sufficient; otherwise, results were set to missing. The entire treatment period was considered evaluable if at least one inter-visit period was evaluable.	
Data are reported as:	Arithmetic Means and 95% confidence interval (CI).	
Endpoint values – Safety Set		

Baseline	**CHF5993 800/24/50 µg pMDI HFA-152a (T)**
	- N° of participants with data / N° of participants with T: 367/368
	- Mean (Std Dev): 0.300 (0.351)
	  - CI 95% lower limit: 0.264;
	  - CI 95% upper limit: 0.336.
	- Median (Min, Max): 0.163 (0.00, 1.98)
		CHF5993 800/24/50 µg pMDI HFA-134a (R)
		- N° of participants with data / N° of participants with R: 185/185
		- Mean (Std Dev): 0.316 (0.384)
		  - CI 95% lower limit: 0.260;
		  - CI 95% upper limit: 0.371.
		Median (Min, Max): 0.170 (0.00, 2.00)

Day 1 – Day 7	**CHF5993 800/24/50 µg pMDI HFA-152a (T)**
	- N° of participants with data / N° of participants with T: 364/368
	- Mean (Std Dev): 0.257 (0.333)
	  - CI 95% lower limit: 0.223;
	  - CI 95% upper limit: 0.291.
	Median (Min, Max): 0.109 (0.00, 1.63)
		CHF5993 800/24/50 µg pMDI HFA-134a (R)
		- N° of participants with data / N° of participants with R: 184/185
		- Mean (Std Dev): 0.308 (0.380)
		  - CI 95% lower limit: 0.253;
		  - CI 95% upper limit: 0.364.
		- Median (Min, Max): 0.152 (0.00, 2.00)

Change from Baseline to Day 1 – Day 7	**CHF5993 800/24/50 µg pMDI HFA-152a (T)** - N° of participants with data / N° of participants with T: 363/368 - Mean (Std Dev): -0.044 (0.191)	**CHF5993 800/24/50 µg pMDI HFA-134a (R)** - N° of participants with data / N° of participants with R: 184/185 - Mean (Std Dev): -0.004 (0.167)

	- CI 95% lower limit: -0.064; - CI 95% upper limit: -0.024. - Median (Min, Max): -0.008 (-0.87, 1.47)	- CI 95% lower limit: -0.028; - CI 95% upper limit: 0.020. - Median (Min, Max): 0.000 (-0.64, 0.56)
Day 7 – Week 4	**CHF5993 800/24/50 µg pMDI HFA-152a (T)** - N° of participants with data / N° of participants with T: 361/368 - Mean (Std Dev): 0.255 (0.331) - CI 95% lower limit: 0.221; - CI 95% upper limit: 0.289. - Median (Min, Max): 0.086 (0.00, 1.38)	**CHF5993 800/24/50 µg pMDI HFA-134a (R)** - N° of participants with data / N° of participants with R: 180/185 - Mean (Std Dev): 0.301 (0.383) - CI 95% lower limit: 0.244; - CI 95% upper limit: 0.357. - Median (Min, Max): 0.149 (0.00, 2.00)
Change from Baseline to Day 7 – Week 4	**CHF5993 800/24/50 µg pMDI HFA-152a (T)** - N° of participants with data / N° of participants with T: 360/368 - Mean (Std Dev): -0.048 (0.214) - CI 95% lower limit: -0.070; - CI 95% upper limit: -0.025. - Median (Min, Max): 0.006 (-1.28, 0.87)	**CHF5993 800/24/50 µg pMDI HFA-134a (R)** - N° of participants with data / N° of participants with R: 180/185 - Mean (Std Dev): -0.009 (0.233) - CI 95% lower limit: -0.043; - CI 95% upper limit: 0.025. - Median (Min, Max): 0.000 (-1.43, 0.78)
Week 4 – Week 12	**CHF5993 800/24/50 µg pMDI HFA-152a (T)** - N° of participants with data / N° of participants with T: 358/368 - Mean (Std Dev): 0.243 (0.324) - CI 95% lower limit: 0.210; - CI 95% upper limit: 0.277. - Median (Min, Max): 0.069 (0.00, 1.49)	**CHF5993 800/24/50 µg pMDI HFA-134a (R)** - N° of participants with data / N° of participants with R: 179/185 - Mean (Std Dev): 0.309 (0.395) - CI 95% lower limit: 0.251; - CI 95% upper limit: 0.367. - Median (Min, Max): 0.116 (0.00, 1.99)

Change from Baseline to Week 4 – Week 12	**CHF5993 800/24/50 µg pMDI HFA-152a (T)**
	- N° of participants with data / N° of participants with T: 357/368
	- Mean (Std Dev): -0.056 (0.264)
	  - CI 95% lower limit: -0.084;
	  - CI 95% upper limit: -0.029.
	- Median (Min, Max): -0.011 (-1.76, 0.99)
		CHF5993 800/24/50 µg pMDI HFA-134a (R)
		- N° of participants with data / N° of participants with R: 179/185
		- Mean (Std Dev): -0.013 (0.297)
		  - CI 95% lower limit: -0.056;
		  - CI 95% upper limit: 0.031.
		- Median (Min, Max): 0.000 (-1.43, 0.88)

Over 12 Weeks Treatment Period	**CHF5993 800/24/50 µg pMDI HFA-152a (T)**
	- N° of participants with data / N° of participants with T: 368/368
	- Mean (Std Dev): 0.253 (0.323)
	  - CI 95% lower limit: 0.220;
	  - CI 95% upper limit: 0.286.
	Median (Min, Max): 0.099 (0.00, 1.63)
		CHF5993 800/24/50 µg pMDI HFA-134a (R)
		- N° of participants with data / N° of participants with R: 185/185
		- Mean (Std Dev): 0.303 (0.378)
		  - CI 95% lower limit: 0.248;
		  - CI 95% upper limit: 0.358.
		- Median (Min, Max): 0.144 (0.00, 1.94)

Change from Baseline to Over 12 Weeks Treatment Period	**CHF5993 800/24/50 µg pMDI HFA-152a (T)**
	- N° of participants with data / N° of participants with T: 367/368
	- Mean (Std Dev): -0.046 (0.243)
	  - CI 95% lower limit: -0.071;
	  - CI 95% upper limit: -0.021.
	- Median (Min, Max): -0.006 (-1.47, 1.47)
		CHF5993 800/24/50 µg pMDI HFA-134a (R)
		- N° of participants with data / N° of participants with R: 185/185
		- Mean (Std Dev): -0.013 (0.258)
		  - CI 95% lower limit: -0.050;
		  - CI 95% upper limit: 0.024.
		- Median (Min, Max): 0.000 (-1.32, 0.83)

D.2.11 Eleventh Secondary Endpoint

Title	Change from baseline in ACQ-7 at each study visit.

Description	This secondary safety variable was summarised as the actual values at each available visit and absolute change from baseline at each study visit. The Asthma Control Questionnaire (ACQ-7) consists of 7 items scored from 0 (no impairment) to 6 (maximum impairment). The ACQ-7 score was calculated as the average of all the items and set to missing if any item was unavailable.	
Analysis type and method	Analysis of the secondary safety variables (Safety Set). This secondary safety variable was analysed using descriptive statistics. Baseline ACQ-7 (Day 1) was derived from ACQ-6 questionnaire data for the first six items collected in the eCRF, and the post over-reading pre-bronchodilator FEV_1% predicted for the seventh item, categorized according to predefined thresholds. At subsequent visits, ACQ-7 was derived using ACQ-6 from external data and pre-dose FEV_1 % predicted applying the same scoring rules. Only ACQ-6 assessments performed on the same day as spirometry were considered.	
Data are reported as:	Arithmetic Means and 95% confidence interval (CI).	
Endpoint values – Safety Set		

Baseline	**CHF5993 800/24/50 µg pMDI HFA-152a (T)**
	
	- N° of participants with data / N° of participants with T: 367/368
	- Mean (Std Dev): 0.74 (0.28)
	  - CI 95% lower limit: 0.71;
	  - CI 95% upper limit: 0.77.
	- Median (Min, Max): 0.71 (0.0, 1.6)
		CHF5993 800/24/50 µg pMDI HFA-134a (R)
		
		- N° of participants with data / N° of participants with R: 184/185
		- Mean (Std Dev): 0.78 (0.30)
		  - CI 95% lower limit: 0.74;
		  - CI 95% upper limit: 0.83.
		- Median (Min, Max): 0.79 (0.0, 1.6)

Day 7	**CHF5993 800/24/50 µg pMDI HFA-152a (T)**
	
	- N° of participants with data / N° of participants with T: 361/368
	- Mean (Std Dev): 0.80 (0.44)
	  - CI 95% lower limit: 0.75;
		CHF5993 800/24/50 µg pMDI HFA-134a (R)
		
		- N° of participants with data / N° of participants with R: 184/185
		- Mean (Std Dev): 0.87 (0.49)
		  - CI 95% lower limit: 0.80;

	- CI 95% upper limit: 0.84. - Median (Min, Max): 0.71 (0.0, 2.7)	- CI 95% upper limit: 0.94. - Median (Min, Max): 0.71 (0.0, 2.9)
Change from Baseline to Day 7	**CHF5993 800/24/50 µg pMDI HFA-152a (T)** - N° of participants with data / N° of participants with T: 360/368 - Mean (Std Dev): 0.06 (0.33) - CI 95% lower limit: 0.02; - CI 95% upper limit: 0.09. - Median (Min, Max): 0.00 (-0.9, 1.7)	**CHF5993 800/24/50 µg pMDI HFA-134a (R)** - N° of participants with data / N° of participants with R: 183/185 - Mean (Std Dev): 0.08 (0.38) - CI 95% lower limit: 0.03; - CI 95% upper limit: 0.14. - Median (Min, Max): 0.00 (-0.7, 2.0)
Week 4	**CHF5993 800/24/50 µg pMDI HFA-152a (T)** - N° of participants with data / N° of participants with T: 357/368 - Mean (Std Dev): 0.81 (0.46) - CI 95% lower limit: 0.76; - CI 95% upper limit: 0.86. - Median (Min, Max): 0.71 (0.0, 3.1)	**CHF5993 800/24/50 µg pMDI HFA-134a (R)** - N° of participants with data / N° of participants with R: 182/185 - Mean (Std Dev): 0.91 (0.54) - CI 95% lower limit: 0.83; - CI 95% upper limit: 0.99. - Median (Min, Max): 0.86 (0.0, 3.3)
Change from Baseline to Week 4	**CHF5993 800/24/50 µg pMDI HFA-152a (T)** - N° of participants with data / N° of participants with T: 357/368 - Mean (Std Dev): 0.07 (0.39) - CI 95% lower limit: 0.03; - CI 95% upper limit: 0.11. - Median (Min, Max): 0.00 (-1.3; 2.6)	**CHF5993 800/24/50 µg pMDI HFA-134a (R)** - N° of participants with data / N° of participants with R: 181/185 - Mean (Std Dev): 0.13 (0.46) - CI 95% lower limit: 0.06; - CI 95% upper limit: 0.19. - Median (Min, Max): 0.00 (-1.0, 2.3)
Week 12	**CHF5993 800/24/50 µg pMDI HFA-152a (T)** - N° of participants with data / N° of participants with T: 353/368	**CHF5993 800/24/50 µg pMDI HFA-134a (R)** - N° of participants with data / N° of participants with R: 179/185

	- Mean (Std Dev): 0.84 (0.53)
	  - CI 95% lower limit: 0.79;
	  - CI 95% upper limit: 0.90.
	- Median (Min, Max): 0.71 (0.0, 3.3)
		- Mean (Std Dev): 0.96 (0.63)
		  - CI 95% lower limit: 0.86;
		  - CI 95% upper limit: 1.05.
		- Median (Min, Max): 0.86 (0.0, 4.3)

Change from Baseline to Week 12	**CHF5993 800/24/50 µg pMDI HFA-152a (T)**
	- N° of participants with data / N° of participants with T: 352/368
	- Mean (Std Dev): 0.10 (0.45)
	  - CI 95% lower limit: 0.05;
	  - CI 95% upper limit: 0.15.
	- Median (Min, Max): 0.00 (-0.7, 2.4)
		CHF5993 800/24/50 µg pMDI HFA-134a (R)
		- N° of participants with data / N° of participants with R: 178/185
		- Mean (Std Dev): 0.17 (0.56)
		  - CI 95% lower limit: 0.09;
		  - CI 95% upper limit: 0.25.
		- Median (Min, Max): 0.00 (-1.3, 3.4)

E. ADVERSE EVENTS

E.1 Adverse events information

Adverse events (AEs) were analysed according to the treatment-emergent principle.

Overall, 108 treatment-emergent adverse events (TEAEs) were reported in 71 (19.3%) participants with CHF5993 800/24/50 µg pMDI HFA-152a (T) and 76 TEAEs were reported in 51 (27.6%) participants with CHF5993 800/24/50 µg pMDI HFA-134a (R).
The preferred terms (PTs) reported in >2% of participants in either treatment arm are reported in the table E.4 – Non-Serious TEAEs.
With both treatments, the majority of TEAEs were mild or moderate in intensity and resolved by the end of the study. A total of 3 (0.8%) participants experienced a severe TEAE with T. No severe TEAEs were reported in participants with R. The only severe TEAE to be reported in >1 participant was the PT of asthma: 2 severe TEAEs of asthma were reported in 2 (0.5%) participants with T.
All severe TEAEs resolved or were resolving by the end of the study.

The incidence of treatment-emergent adverse events of particular interest (AEPIs) was low: a total of 16 treatment-emergent AEPIs were reported in 16 (4.3%) participants with T and 10 treatment-emergent AEPIs were reported in 9 (4.9%) participants with R. The PT of asthma was the most reported treatment-emergent AEPI. No severe treatment-emergent AEPIs were considered related to the study treatment. No treatment-emergent AEPI were considered as serious.

The incidence of Adverse drug reactions (ADRs) was low in both treatment arms: 20 ADRs in 11 (3.0%) participants with T and 5 ADRs in 5 (2.7%) participants with R. The PTs reported in >1 participant in either treatment arm was as follows: oral candidiasis, cough, tongue fungal infection and dry mouth. No ADRs were considered serious.

The incidence of ADRs of particular interest was low and comparable between treatment arms: 2 ADRs of particular interest in 2 (0.5%) participants with T and 2 ADRs of particular interest in 2 (1.1%) participants with R. The only ADR of particular interest to be reported in >1 participants in either treatment arm was cough. No ADRs of particular interest were considered serious.

No deaths were reported during the study.

Definitions and Timeframe for reporting AEs	Three categories of AEs were presented and were classified as follows: • Pre-treatment AE: any AEs that started after the informed consent signature and before the first study treatment; • TEAE: any AEs that started on or after the first study treatment intake and up to 1 week after the last dose of study treatment intake; • Post-treatment AE: any AEs that started later than 1 week after the last dose of study treatment. Adverse events of particular interest (AEPIs) included cough, dysphonia, paradoxical bronchospasm, hypersensitivity reactions, severe asthma exacerbations defined according to American Thoracic Society/European Respiratory Society criteria. AEPIs were grouped according to the TEAE SOC (system organ class) and PT. ADRs were defined as “noxious and unintended response to an IMP related to any dose administered”.
Dictionary used	MedDRA version 26.0

E.2 Adverse event reporting group

The safety set included 553 participants overall, presented by treatment arm (T and R).

E.3 Serious TEAEs

	CHF5993 800/24/50 µg pMDI HFA-152a (T)	**CHF5993 800/24/50 µg pMDI HFA-134a (R)**
Total participants affected/exposed N° of events	4/368 (1.1%) 4	0

Infections and Infestations		
COVID-19		
Total participants affected/exposed N° of events	1/368 (0.3%) 1	0
Injury, poisoning and procedural complications		
Procedural haemorrhage		
Total participants affected/exposed N° of events	1/368 (0.3%) 1	0
Musculoskeletal and connective tissue disorders		
Back Pain		
Total participants affected/exposed N° of events	1/368 (0.3%) 1	0
Nervous System Disorders		
Ischaemic stroke		
Total participants affected/exposed N° of events	1/368 (0.3%) 1	0

E.4 Non-Serious TEAEs

	CHF5993 800/24/50 µg pMDI HFA-152a (T)	**CHF5993 800/24/50 µg pMDI HFA-134a (R)**
Total participants affected/exposed N° of events	68/368 (18.5%) 104	51/185 (27.6%) 76
Infections and Infestations		
Total participants affected/exposed N° of events	35/368 (9.5%) 42	30/185 (16.2%) 33
Nasopharyngitis		
Total participants affected/exposed N° of events	16/368 (4.3%) 17	10/185 (5.4%) 11
Nervous System Disorders		
Total participants affected/exposed N° of events	8/368 (2.2%) 8	7/185 (3.8%) 7
Headache		
Total participants affected/exposed N° of events	7/368 (1.9%) 7	6/185 (3.2%) 6
Respiratory, Thoracic and Mediastinal Disorders		
Total participants affected/exposed	25/368 (6.8%) 27	13/185 (7.0%) 18

N° of events		
Asthma		
Total participants affected/exposed N° of events	19/368 (5.2%) 20	9/185 (4.9%) 9

E.5 Non-Serious ADRs

	CHF5993 800/24/50 µg pMDI HFA-152a (T)	**CHF5993 800/24/50 µg pMDI HFA-134a (R)**
Total participants affected/exposed N° of events	11/368 (3.0%) 20	5/185 (2.7%) 5
Gastrointestinal disorders		
Dry mouth		
Total participants affected/exposed N° of events	2/368 (0.5%) 2	0
Odynophagia		
Total participants affected/exposed N° of events	1/368 (0.3%) 1	0
Oesophageal discomfort		
Total participants affected/exposed N° of events	1/368 (0.3%) 1	0
Infections and Infestations		
Oral candidiasis		
Total participants affected/exposed N° of events	2/368 (0.5%) 2	2/185 (1.1%) 2
Tongue fungal infection		
Total participants affected/exposed N° of events	2/368 (0.5%) 2	0
Oral fungal infection		
Total participants affected/exposed N° of events	1/368 (0.3%) 1	0
Oropharyngeal candidiasis		
Total participants affected/exposed N° of events	0	1/185 (0.5%) 1
Oropharyngitis fungal		
Total participants affected/exposed N° of events	1/368 (0.3%) 1	0

Musculoskeletal and connective tissue disorders		
Muscle spasms	1/368 (0.3%) 1	0
Nervous System Disorders		
Headache		
Total participants affected/exposed N° of events	1/368 (0.3%) 1	0
Tremor		
Total participants affected/exposed N° of events	1/368 (0.3%) 1	0
Psychiatric disorders		
Anxiety		
Total participants affected/exposed N° of events	1/368 (0.3%) 1	0
Insomnia		
Total participants affected/exposed N° of events	1/368 (0.3%) 1	0
Respiratory, Thoracic and Mediastinal Disorders		
Cough		
Total participants affected/exposed N° of events	2/368 (0.5%) 2	1/185 (0.5%) 1
Dry throat		
Total participants affected/exposed N° of events	1/368 (0.3%) 1	0
Dysphonia		
Total participants affected/exposed N° of events	0	1/185 (0.5%) 1
Oropharyngeal discomfort		
Total participants affected/exposed N° of events	1/368 (0.3%) 1	0
Throat irritation		
Total participants affected/exposed N° of events	1/368 (0.3%) 1	0

E.6 Non-Serious TEAEs of Particular Interest

	CHF5993 800/24/50 µg pMDI HFA-152a (T)	**CHF5993 800/24/50 µg pMDI HFA-134a (R)**
Total participants affected/exposed N° of events	16/368 (4.3%) 16	9/185 (4.9%) 10

Respiratory, Thoracic and Mediastinal Disorders		
Asthma		
Total participants affected/exposed N° of events	14/368 (3.8%) 14	7/185 (3.8%) 7
Cough		
Total participants affected/exposed N° of events	2/368 (0.5%) 2	2/185 (1.1%) 2
Dysphonia		
Total participants affected/exposed N° of events	0	1/185 (0.5%) 1

E.7 Adverse Drug Reactions of Particular Interest

	CHF5993 800/24/50 µg pMDI HFA-152a (T)	**CHF5993 800/24/50 µg pMDI HFA-134a (R)**
Total participants affected/exposed N° of events	2/368 (0.5%) 2	2/185 (1.1%) 2
Respiratory, Thoracic and Mediastinal Disorders		
Cough		
Total participants affected/exposed N° of events	2/368 (0.5%) 2	1/185 (0.5%) 1
Dysphonia		
Total participants affected/exposed N° of events	0	1/185 (0.5%) 1

F. ADDITIONAL INFORMATION

F.1 Global Substantial Modifications

The study protocol was revised (Versions 1.0, 2.0, and 4.0). All sites initiated the study under Version 2.0. Version 4.0 was submitted by the Sponsor as a non-substantial amendment; however, in Serbia it was requested and reviewed as a substantial amendment, while remaining classified as non-substantial in the Sponsor's records.

F.2 Global Interruptions and re-starts

Not applicable

F.3 Limitations, addressing sources of potential bias and imprecisions and Caveats

Not applicable

F.4 Declaration on the accuracy of the submitted information

The Sponsor certifies that the information provided in this Report is accurate to the best of their knowledge.