2. SYNOPSIS

Name of Company: **Chiesi Farmaceutici S.p.A.**	**Individual Study Table Referring to Part of the Dossier**	*(for National Authority Use only)*
Name of Finished Product: **Medium Strength (MS) CHF 5993** **High Strength (HS) CHF 5993 (Trimbow®)**	**Volume:**	
Name of Active Ingredient: **MS CHF 5993: Beclometasone dipropionate (BDP) 100 µg + formoterol fumarate (FF) 6 µg + glycopyrronium bromide (GB) 12.5 µg** **HS CHF 5993: BDP 200 µg + FF 6 µg + GB 12.5 µg**	**Page:**	

Title of Study: A 26 week, randomized, double blind, multinational, multicentre, active controlled, 2-arm parallel group trial comparing CHF 5993 100/6/12.5 µg pMDI (fixed combination of extrafine formulation of beclometasone dipropionate plus formoterol fumarate plus glycopyrronium bromide) to CHF 1535 200/6 µg pMDI (fixed combination of extrafine formulation of beclometasone dipropionate plus formoterol fumarate) in subjects with asthma uncontrolled on medium doses of inhaled corticosteroids in combination with long-acting ß2-agonists (MiSTIC)

Investigators: 146 recruiting Investigators in 16 countries

Study Centre(s): Multicentre; 209 centres were initiated, of which 146 centres were active

Publication (Reference): Kostikas K, Topole E, Singh D, et al. The MiSTIC Study Design: Medium Strength Triple Therapy vs High Strength ICS/LABA for Adult Patients With Asthma Uncontrolled on Medium Strength ICS/LABA (abstract). Am J Respir Crit Care Med 2023;207:A1310.

Studied Period: First Subject First Visit (FSFV): 25 Feb 2022 (main phase) Last Subject Last Visit (LSLV): 16 Apr 2024 (main phase)	**Phase of Development:** IV

Objectives:

Primary/main objectives

Primary objective – main phase

To demonstrate the superiority of medium strength (MS) BDP/FF/GB pressurised metered dose inhaler (pMDI) (MS CHF 5993 pMDI; 100/6/12.5 µg two puffs twice daily [BID]) compared to high strength (HS) BDP/FF pMDI (HS CHF 1535 pMDI; 200/6 µg, two puffs BID) in terms of the proportion of subjects exhibiting no persistent airflow limitation (NPAL) on average over 26 weeks of treatment in the study sub-population with persistent airflow limitation (PAL) at screening.

- A subject was defined as having PAL at screening if their post-bronchodilator (salbutamol) forced expiratory volume in the 1st second (FEV_1)/forced vital capacity (FVC) ratio was <0.7.
- A subject was defined as having NPAL during the treatment period if the mean of their 2-hour post-dose FEV_1/FVC ratios collected during the 26-week treatment period (i.e., from Week 0 to Week 26) was ≥0.7.

The attributes defining the main estimand associated with the primary objective are included in the clinical study report (CSR) body.

Main objectives – Open Label Extension (OLE) phase

Subjects were assessed in four different cohorts, depending on the study treatment taken in the main phase and on the category of asthma control defined at the start of the OLE phase at Week 26. The main objectives of the OLE phase were:

- To assess the proportion of subjects whose asthma remained 'Adequately Controlled' on treatment with MS BDP/FF/GB (MS CHF 5993 pMDI) at the end of the OLE phase (i.e., Week 50) in the subgroup of subjects with previously 'Adequately Controlled Asthma' on HS BDP/FF (HS CHF 1535 pMDI) at the end of the main phase (i.e., Week 26; Cohort 1);
- To assess the proportion of subjects whose asthma became 'Adequately Controlled' on HS BDP/FF/GB (HS CHF 5993 pMDI) at the end of the OLE phase (i.e., Week 50) in the subgroup of subjects with previously 'Uncontrolled Asthma' on MS BDP/FF/GB (MS CHF 5993 pMDI) at the end of the main phase (i.e., Week 26; Cohort 2);
- To assess the proportion of subjects whose asthma became 'Adequately Controlled' on HS BDP/FF/GB (HS CHF 5993 pMDI) at the end of the OLE phase (i.e., Week 50) in the subgroup of subjects with previously 'Uncontrolled Asthma' on HS BDP/FF (HS CHF 1535 pMDI) at the end of the main phase (i.e., Week 26; Cohort 3);
- To assess the proportion of subjects whose asthma remained 'Adequately Controlled' with continuation of treatment with MS BDP/FF/GB (MS CHF 5993 pMDI) at the end of the OLE phase (i.e., Week 50), in the subgroup of subjects with previously 'Adequately Controlled Asthma' on MS BDP/FF/GB (MS CHF 5993 pMDI) at the end of the main phase (i.e., Week 26; Cohort 4).

The attributes defining the main estimands associated with the four main objectives in the OLE phase are included in the clinical study protocol.

Secondary/other objectives

Key secondary objective – main phase

To demonstrate the superiority of MS BDP/FF/GB pMDI (MS CHF 5993 pMDI; 100/6/12.5 µg two puffs BID) compared to HS BDP/FF pMDI (HS CHF 1535 pMDI; 200/6 µg two puffs BID) in terms of change from baseline in pre-dose FEV_1 at Week 26 in the study sub-population meeting the PAL criterion at screening.

The attributes defining the main estimand associated with the key secondary objective are included in the CSR body.

Other secondary objectives – main phase

- To compare the study treatments on other lung function assessments, clinical outcomes, risk of exacerbations in the study sub-population meeting the PAL criterion at screening and in the overall study population;
- To assess the safety and tolerability of the study treatments in the study sub-population meeting the PAL criterion at screening and in the overall study population.

Other objectives – OLE phase

- To assess other lung function parameters, inflammatory parameters, clinical outcomes, risk of asthma exacerbations, health economics outcomes in the four cohorts of subjects during the OLE phase;
- To assess the safety and tolerability of the study in the four cohorts of subjects during the OLE phase.

Methodology *(Study Design):*

This study comprised a randomised, double-blind main phase and an optional OLE phase. Of note, this study was terminated prematurely per the Sponsor's decision due to a substantial delay in recruitment and its impact on timelines, and it was decided to prepare an abbreviated CSR.

Main phase

The main phase of this study was a Phase IV, multinational, multicentre, randomised, double-blind, active-controlled, two-arm parallel group study in adult subjects with asthma uncontrolled on medium dose of inhaled corticosteroids (ICS) in combination with a long-acting β_2-agonist (LABA) who had at least one asthma exacerbation in the past 3 years. The main phase was designed to demonstrate the superiority of MS CHF 5993 pMDI (100/6/12.5 µg BDP/FF/GB, two puffs BID) compared to HS CHF 1535 pMDI (200/6 µg BDP/FF, two puffs BID) in terms of the proportion of subjects exhibiting NPAL on average over 26 weeks of treatment in the study sub-population with PAL at screening. Following the decision to terminate the study prematurely, subjects ongoing in the main phase were to complete the evaluation.

The main phase comprised a 1-week pre-screening period, a 2-week run-in period, a 26-week treatment period and a 1-week post-treatment follow-up period, applicable only for subjects not enrolled in the OLE phase. A total of seven clinic visits (Visit [V]0 to V6) and one follow-up call (for subjects not enrolled in the OLE phase) were performed in the main phase. The pre-screening visit (V0, Week -3) was planned to occur no more than 7 days prior to the screening visit (V1, Week -2), followed by a 2-week, open-label run-in period during which the subjects received MS CHF 1535 pMDI (100/6 µg two puffs BID; total daily dose [TDD] 400/24 µg BDP/FF).

At the randomisation visit (V2, Week 0), eligible subjects were randomised in a 1:1 ratio to one of the following two treatment groups and received their first study treatment:

- MS CHF 5993 pMDI (100/6/12.5 µg two puffs BID; TDD 400/24/50 µg BDP/FF/GB);
- HS CHF 1535 pMDI (200/6 µg two puffs BID; TDD 800/24 µg BDP/FF).

Salbutamol (100 µg/puff) was used as rescue medication as needed for breakthrough asthma symptoms.

During the 26-week treatment period, clinic/hospital visits were performed after 4 weeks (V3), 12 weeks (V4), 22 weeks (V5) and 26 weeks (V6). For those subjects not enrolled in the OLE phase, a follow-up call took place 1 week after the last study visit (V6, Week 26) to check safety and the subjects' status. An Early Treatment Discontinuation (ETD) visit was performed in case a subject was withdrawn before the end of the treatment period.

During the run-in and treatment periods, efficacy and safety measures were taken at each visit. Additionally, subjects completed an electronic diary (e-Diary) for recording of asthma symptoms, treatment compliance and rescue medication intake daily and performed assessments of peak expiratory flow and spirometry (only subjects enrolled prior to protocol Version 4.0) at home.

OLE phase

At the end of the main phase, it was planned that subjects could opt to enrol in the OLE phase until the target sample size was reached. The OLE phase was an exploratory, open-label, non-randomised, multinational, multicentre, two-arm, parallel-group extension study. The OLE phase employed a partially decentralised approach with the aim to monitor subjects at home to reduce the burden for subjects. Following the decision to terminate the study prematurely, subjects ongoing in the OLE phase were to terminate the study and attend the ETD visit within 1 month.

Asthma control at the end of the main phase (i.e., V6 at Week 26), was classified for each subject as either 'Adequately Controlled Asthma' or 'Uncontrolled Asthma' based on Asthma Control Questionnaire© (ACQ)-6 results, lung function and exacerbations. Specifically, asthma was considered adequately controlled if all of the following three criteria were met: ACQ-6 score <1.5 at V5 (Week 22) and V6 (Week 26); absence of severe asthma exacerbation from V4 (Week 12) to V6 (Week 26); absence of ≥10% drop in pre-dose FEV_1 at V6 (Week 26) compared to baseline (Week 0), while it was considered uncontrolled if at least one of these criteria was not met. Subjects who discontinued from study treatment before the end of the main phase (Week 26) or who could not be included in one of the two categories were not to be considered for the OLE phase.

The treatment allocation in the OLE phase was planned to be based on the asthma control status at the end of the main phase (V6 at Week 26):

- Subjects assessed as having 'Adequately Controlled Asthma' were to be assigned to MS CHF 5993 pMDI (100/6/12.5 µg two puffs BID; TDD 400/24/50 µg BDP/FF/GB);
- Subjects assessed as having 'Uncontrolled Asthma' were to be assigned to HS CHF 5993 pMDI (200/6/12.5 µg two puffs BID; TDD 800/24/50 µg BDP/FF/GB).

Subjects were planned to be assessed in four cohorts, depending on the study treatment taken in the main phase and on the asthma control status defined at the end of the main phase at Week 26. The OLE phase was designed to assess the proportions of subjects whose asthma became or remained 'Adequately Controlled' at the end of the OLE phase, with respect to the end of the main phase, in each of the four cohorts.

The OLE phase was planned to comprise a 24-week open-label treatment period and a 1-week post-treatment follow-up period. A total of five visits (three on site and two remote) from $V6^{OLE}$ to V10 and one follow-up call were planned.

The enrolment visit of the OLE phase ($V6^{OLE}$) occurred on the same day as V6 of the main phase (Week 26), to evaluate OLE phase-specific screening criteria after all assessments for the main phase had been performed. Subjects eligible for the OLE phase were to be categorised according to their asthma control status and assigned treatment accordingly, and study treatment kits were dispensed. Remote visits were planned to be performed at V7 (Week 30, 4 weeks after the start of the OLE phase) and V9 (Week 46, 20 weeks after the start of OLE the phase) in countries where this was allowed per local regulations (in the form of video call with the Investigator via a Decentralised Clinical Trial platform). Otherwise, on-site visits were planned to be performed instead. Clinic visits were planned to be performed at V8 (Week 38, 12 weeks after the start of the OLE phase), where subjects were provided with study treatment resupply, and at V10 (Week 50, 24 weeks after the start of OLE phase). An ETD visit was performed in case a subject was withdrawn before the end of the treatment period.

A safety follow-up phone call was performed 1 week after V10 or the ETD visit to check the status of unresolved adverse events (AEs) and to record any new AEs that occurred after the last visit, as well as the related concomitant medications.

During the OLE phase treatment period, efficacy and safety measures were to be taken at each visit. Additionally, subjects were asked to complete an e-Diary for recording of asthma symptoms, treatment compliance and rescue medication intake daily, perform home spirometry (only subjects enrolled prior to protocol Version 4.0) and complete the ACQ-6.

Number of Subjects *(Planned and Analysed)*:

Main phase

A total of 1400 subjects were planned to be randomised in a 1:1 ratio to either MS CHF 5993 pMDI or HS CHF 1535 pMDI (i.e., 700 subjects per group), with a planned inclusion of 65% of subjects with PAL and 35% of subjects with NPAL per group.

The number of subjects in the main phase of the study is summarised in the table below.

	MS CHF 5993 pMDI			HS CHF 1535 pMDI			Overall		
	PAL at screening	NPAL at screening	Total	PAL at screening	NPAL at screening	Total	PAL at screening	NPAL at screening	Total
Randomised Set, n	93	64	157	79	82	161	172	146	318
Safety Set, n	92	64	156	78	82	160	170	146	316
ITT Set, n	92	64	156	78	82	160	170	146	316

HS = High Strength; ITT = Intention-to-treat; MS = Medium Strength; NPAL = No persistent airflow limitation; PAL = Persistent airflow limitation; pMDI = Pressurised metered dose inhaler.
n = Number of subjects in each set.

OLE phase

It was anticipated that the maximum number of subjects included in the OLE phase would not exceed 800 subjects.

The number of subjects in the OLE phase of the study is summarised in the table below.

	MS CHF 5993 pMDI	HS CHF 5993 pMDI	Overall
Allocated Set, n	–	–	70
Safety Set, n	28	42	70
ITT Set, n	27	43	70

HS = High Strength; ITT = Intention-to-treat; MS = Medium Strength; pMDI = Pressurised metered dose inhaler.
n = Number of subjects in each set.

Diagnosis and Main Criteria for Inclusion:

Main phase

Eligible subjects included male or female subjects aged ≥18 and ≤75 years (with an exception for the Netherlands where no upper age limit was set, based on local requirements) with a documented diagnosis of permanent asthma for at least 1 year before the age of 40 years and on stable treatment with medium dose ICS/LABA, who had evidence of poorly controlled or uncontrolled asthma based on an ACQ-7 score ≥1.5. Subjects had to have a pre-bronchodilator FEV_1 <80% of the predicted normal value after appropriate washout from bronchodilators; bronchodilator responsiveness demonstrated by an increase in FEV_1 >12% and >200 mL over baseline within 30 minutes after inhaling 400 µg of salbutamol pMDI; a post-bronchodilator FEV_1/FVC ratio ≥0.5 within 30 minutes after inhaling 400 µg of salbutamol pMDI and a documented history of one or more asthma exacerbations in the last 3 years prior to screening.

OLE phase

To be eligible for the optional OLE phase, subjects who were willing to participate had to have completed the main phase and have available data to allow classification in one of the two categories 'Adequately Controlled Asthma' and 'Uncontrolled Asthma' at the end of the main phase (Week 26). Subjects also had to have a main phase study treatment compliance ≥70%.

Test Product, Dose and Mode of Administration, Batch Number:

Main phase

Test product: MS CHF 5993 pMDI fixed dose combination of 100/6/12.5 µg BDP/FF/GB

Dose: 100/6/12.5 µg per actuation, two puffs BID; TDD 400/24/50 µg BDP/FF/GB

Mode of administration: pMDI; if subjects were used to inhaling their pMDI asthma medications with a spacer device, required a spacer device to properly use the pMDI or were experiencing difficulties when switching from a different inhaler type, they used the AeroChamber Plus™.

Batch numbers:

Campaign	MS CHF 5993 pMDI	
	Batch number	Expiry date
1	1135485	30 Apr 2023
2	1143951	30 Nov 2023
3	1154985	31 May 2024
4	1175091	31 May 2025

MS = Medium Strength; pMDI = Pressurised metered dose inhaler.

OLE phase

Test products:

- MS CHF 5993 pMDI fixed dose combination of 100/6/12.5 µg BDP/FF/GB
- HS CHF 5993 pMDI fixed dose combination of 200/6/12.5 µg BDP/FF/GB

Doses:

- MS CHF 5993 pMDI: 100/6/12.5 µg per actuation, two puffs BID; TDD 400/24/50 µg BDP/FF/GB
- HS CHF 5993 pMDI: 200/6/12.5 µg per actuation, two puffs BID; TDD 800/24/50 µg BDP/FF/GB

Mode of administration: pMDI

Batch numbers:

Campaign	MS CHF 5993 pMDI		HS CHF 5993 pMDI	
	Batch number	Expiry date	Batch number	Expiry date
1	1146575	31 Dec 2023	1147737	31 Dec 2023
2	1159268	31 Aug 2024	1159751	31 Jul 2024

HS = High Strength; MS = Medium Strength; pMDI = Pressurised metered dose inhaler.

Duration of Treatment:

Main phase

A 2-week run-in period on MS CHF 1535 pMDI (100/6 µg two puffs BID; TDD 400/24 µg BDP/FF) followed by a 26-week treatment period on randomised treatment.

OLE phase

A 24-week open-label treatment period.

Reference Therapy, Dose and Mode of Administration, Batch Number:

Main phase

Test product: HS CHF 1535 pMDI fixed dose combination of 200/6 µg BDP/FF

Dose: 200/6 µg per actuation, two puffs BID; TDD 800/24 µg BDP/FF

Mode of administration: pMDI; if subjects were used to inhaling their pMDI asthma medications with a spacer device, required a spacer device to properly use the pMDI or were experiencing difficulties when switching from a different inhaler type, they used the AeroChamber Plus™.

Batch numbers:

Campaign	HS CHF 1535 pMDI	
	Batch number	Expiry date
1	1134985	31 Mar 2023
2	1144370	31 Oct 2023
3	1154394	30 Apr 2024
4	1175082	31 Mar 2025

HS = High Strength; pMDI = Pressurised metered dose inhaler.

OLE phase

No reference product was included in the OLE phase.

Criteria for Evaluation:

Efficacy:

The efficacy variables are presented as planned in the clinical study protocol and modified in the statistical analysis plan (SAP) Version 1.0.

Primary/main efficacy variables

Primary efficacy variable – main phase

- Proportion of subjects exhibiting NPAL status on average over 26 weeks of treatment in the study sub-population meeting the PAL criterion at screening.

Definitions of PAL at screening and NPAL over 26 weeks of treatment are provided with the primary objective above and further details on the calculation are included in the statistical methods below.

Main efficacy variables – OLE phase

Main efficacy variables for the OLE phase are not included in this abbreviated CSR but are provided in the clinical study protocol and the SAP.

Secondary efficacy variables

Key secondary efficacy variable – main phase

- Change from baseline in pre-dose morning FEV_1 at Week 26 in the study sub-population meeting the PAL criterion at screening.

Other secondary efficacy variables – main phase

Other secondary efficacy variables for the main phase are not included in this abbreviated CSR but are provided in the clinical study protocol and the SAP.

Other efficacy variables – OLE phase

Other secondary efficacy variables for the OLE phase are not included in this abbreviated CSR but are provided in the clinical study protocol and the SAP.

Exploratory variables

Exploratory variables for the main and OLE phases are not included in this abbreviated CSR but are provided in the clinical study protocol and the SAP.

Safety:

Main phase

- Treatment-emergent adverse events (TEAEs), adverse drug reactions (ADRs), serious TEAEs, serious related TEAEs, TEAEs leading to study treatment discontinuation, and TEAEs leading to death;
- Vital signs (systolic blood pressure [SBP] and diastolic blood pressure [DBP]);
- 12-lead electrocardiogram (ECG) parameters: heart rate (HR), Fridericia's corrected QT interval (QTcF), PR interval (PR) and QRS interval (QRS);
- Standard haematology and blood chemistry.

OLE phase

- TEAEs, ADRs, serious TEAEs, serious related TEAEs, TEAEs leading to study treatment discontinuation, and TEAEs leading to death;
- Vital signs (SBP and DBP);
- Standard haematology and blood chemistry.

Statistical Methods:

The following analysis sets were considered for analysis:

- The Intention-to-treat (ITT) Set was used for analysis of all efficacy variables and was defined for the main and OLE phases of the study as follows:
  - Main phase: all randomised subjects who received at least one dose of study treatment in the main phase. In case of deviation between as-randomised treatment and treatment actually received, the subject was reported under the randomised treatment group for all analyses performed on the ITT Set (i.e., an as-randomised analysis was performed). The sub-population of the ITT Set composed of subjects included in the ITT Set who met the PAL criterion at screening was also used for efficacy analyses;
  - OLE phase: all subjects eligible for the OLE phase who received at least one dose of study treatment in the OLE phase. In case of deviation between planned treatment in the OLE phase and treatment received, the subject was reported under the open label treatment group for all analyses performed on the ITT Set.
- The Safety Set was used in the analysis of all safety variables and was defined for the main and OLE phases of the study as follows:
  - Main phase: all randomised subjects who received at least one dose of study treatment in the main phase. In case of deviation between as-randomised treatment and treatment actually received, the treatment actually received was used in the analyses (i.e., an as-treated analysis was performed);
  - OLE phase: all subjects eligible for the OLE phase who received at least one dose of study treatment in the OLE phase. In case of deviation between as-allocated treatment and treatment actually received, the treatment actually received was used in the analyses (i.e., an as-treated analysis was performed).

Efficacy analysis

For the main phase, the primary and key secondary efficacy endpoints were tested for statistical significance following a hierarchical strategy to control the familywise Type I error rate using the main estimand. Each test was considered confirmatory only if the tests on all the previous steps were successful. The hierarchy for the primary and key secondary efficacy endpoints was as follows:

- Step 1: primary endpoint using the main estimand;
- Step 2: key secondary endpoint using the main estimand.

For an individual visit, PAL status was defined as 2-hour post-dose FEV_1/FVC ratio <0.7. A subject was defined as exhibiting PAL over 26 weeks of treatment if the average value of the 2-hour post-dose FEV_1/FVC ratios collected during the 26-week treatment period (i.e., all the FEV_1/FVC data collected from Week 0 to Week 26, excluding unscheduled visits) was <0.7.

For an individual visit, NPAL status was defined as 2-hour post-dose FEV_1/FVC ratio ≥0.7.

A subject was defined as exhibiting NPAL over 26 weeks of treatment if the average value of the 2-hour post-dose FEV_1/FVC ratios collected during the 26-week treatment period (i.e., all the FEV_1/FVC data collected from Week 0 to Week 26, excluding unscheduled visits) was ≥0.7.

Primary efficacy variable – main phase

The primary efficacy variable for the main phase was the proportion of subjects exhibiting NPAL status on average over 26 weeks of treatment in the study sub-population meeting the PAL criterion at screening (ITT Set). The attributes defining the main estimand associated with the primary efficacy variable of the main phase of the study are presented in the body CSR. In summary, the analysis of the primary efficacy variable, considering the main estimand, included the collected on-treatment 2-hour post-dose FEV_1/FVC values (i.e., data collected until the study treatment discontinuation), the imputed 2-hour post-dose FEV_1/FVC values using the missing at random (MAR) assumption (for both the missing on-treatment and all the off-treatment assessments) and the ITT sub-population of subjects meeting the PAL criterion at screening.

All off-treatment 2-hour post-dose FEV_1/FVC values (i.e., collected after study treatment discontinuation) were considered as missing and were not used in this analysis. All missing 2-hour post-dose FEV_1/FVC values (i.e., both missing on-treatment values and all off-treatment values) were imputed considering the MAR assumption in both treatment groups; this approach targeted the treatment effect that would have been observed if all subjects had continued the study treatment for the whole 26-week study duration, thus targeting a hypothetical estimand. Regarding the intercurrent events (ICEs) 'Use of non-permitted medication and other important protocol deviations' and 'Wrong study treatment intake' in the main estimand, the analysis of the primary efficacy variable aimed to target the treatment effect regardless of whether or not the ICE occurred, thus targeting a treatment policy strategy.

The proportion of subjects exhibiting NPAL status over 26 weeks of treatment in the study sub-population meeting the PAL criterion at screening was analysed using a logistic regression model including treatment and region as factors and baseline FEV_1/FVC value (i.e., Week 0, pre-dose) as covariate. The odds ratio to exhibit NPAL over 26 weeks of treatment with its 95% Wald confidence interval (CI) and corresponding p-value were estimated by the model.

Main efficacy variables – OLE phase

The main efficacy variables for the OLE phase were not analysed.

Key secondary efficacy variable – main phase

The key secondary efficacy variable for the main phase was the change from baseline in pre-dose morning FEV_1 at Week 26 in the study sub-population meeting the PAL criterion at screening (ITT Set). The attributes defining the main estimand associated with the key secondary efficacy variable of the main phase of the study are presented in the body CSR. In summary, the analysis of the key secondary efficacy variable considering the main estimand included the collected on-treatment pre-dose FEV_1 values (i.e., data collected until the study treatment discontinuation) and the ITT sub-population of subjects meeting the PAL criterion at screening. The strategies for the defined ICEs were in line with the ones described for the main estimand associated with the primacy efficacy variable.

All off-treatment pre-dose FEV_1 values (i.e., collected after study treatment discontinuation) were considered as missing and were not used in this analysis. All missing pre-dose FEV_1 values (i.e., both missing on-treatment values and all off-treatment values) were managed by the mixed model for repeated measures (MMRM; i.e., no imputation was performed in this analysis). As the MMRM relied on MAR assumptions for missing data, this approach targeted the treatment effect

that would have been observed if all subjects had continued the study treatment for the whole 26-week study duration, thus targeting a hypothetical estimand. Regarding the ICEs 'Use of non-permitted medication and other important protocol deviations' and 'Wrong study treatment intake' in the main estimand, the analysis of the key secondary efficacy variable aimed to target the treatment effect regardless of whether or not the ICE occurred, thus targeting a treatment policy strategy. No imputation procedure was carried out.

The change from baseline in pre-dose FEV_1 at Week 26 was analysed in the ITT sub-population of subjects meeting the PAL criterion at screening using a linear MMRM. An unstructured covariance matrix was assumed. The model estimated the adjusted means in each treatment group, adjusted mean difference between treatments and their 95% CIs at each study visit.

Other/secondary efficacy variables

The other/secondary efficacy variables for the main and OLE phase were not analysed.

Safety analysis

Descriptive analysis of AEs for the main phase was performed on the Safety Set using on-treatment data only. Pre-treatment AEs, TEAEs and post-treatment AEs (applicable only for subjects not enrolled in the OLE phase) were presented separately. The number of events and the number and percentage of subjects experiencing events were summarised by treatment group for TEAEs, serious TEAEs, ADRs, non-serious AEs, serious ADRs, severe AEs, AEs leading to discontinuation and AEs leading to death. The number of subjects diagnosed with coronavirus disease 2019 (COVID-19) was also summarised in the Safety Set. Post-treatment AEs were summarised similarly for subjects not enrolled in the OLE phase. The number and percentage of subjects with at least one event and the number of AEs were presented by system organ class (SOC) and preferred term (PT) by treatment group for TEAEs, serious TEAEs, ADRs, non-serious AEs, serious ADRs, severe AEs, AEs leading to discontinuation, AEs leading to death and post-treatment AEs, and by treatment group in descending order of PT for the most common TEAEs (reported in ≥5% of subjects in any treatment group).

Comparative analysis of AEs was performed on the Safety Set using on-treatment data only. The number of subjects who experienced at least one TEAE, serious TEAE, ADR, serious ADR, severe AE, AE leading to discontinuation and AE leading to death was compared between treatment groups in terms of risk difference, calculated considering the crude proportion of subjects with the selected event in the two treatment groups. The 95% CIs for the risk difference was calculated using the Newcombe Hybrid Score method. The numbers of subjects who experienced at least one TEAE by SOC, TEAE by PT, serious TEAE by SOC and serious TEAE by PT were compared between treatment groups using the same methodology as described above. These comparative analyses were not to be performed if the total number of subjects with the event in the overall Safety Set was <10.

Adverse events which occurred during the OLE phase were only listed and planned summary statistics were not performed.

Actual values and changes from baseline for vital signs were summarised by treatment group in the Safety Set using on-treatment data only with descriptive statistics and the 95% CI of the mean for both phases. Actual values for laboratory parameters and changes from baseline (if repeated assessments were performed) for the main phase were displayed using summary statistics and the 95% CI of the mean at each scheduled visit in the Safety Set using on-treatment data only. Results of urine pregnancy tests and OLE laboratory data were only listed.

Data collected on physical examination during the study were only listed.

Pre-dose 12-lead ECG parameters for the main phase were summarised by treatment in the Safety Set using on-treatment data only, with descriptive statistics and the 95% CI of the mean. The number and percentage of males with a QTcF >450 ms, >480 ms and >500 ms and of females with a QTcF 470 ms and >500 ms was also displayed.

Summary – Conclusions:

Efficacy Results:

Due to a substantial delay in recruitment and its impact on timelines, this study was terminated prematurely per the Sponsor's decision. Only 318 subjects (of 1400 subjects initially planned) were randomised for the main phase and 70 subjects (of up to 800 subjects initially planned) were included in the OLE phase. In the main phase, only 172 subjects (of 910 initially planned) met the PAL criterion at screening, constituting the study sub-population for the main analyses. The majority of the 318 subjects randomised to MS CHF 5993 pMDI (100/6/12.5 µg BDP/FF/GB) (157 subjects) and HS CHF 1535 pMDI (200/6 µg BDP/FF) (161 subjects) in the main phase completed the study (142 [90.4%] and 146 [90.7%] subjects, respectively). Only few subjects completed the OLE phase; the main reason for early discontinuation in the OLE phase in nearly all subjects was the early termination of the study by the Sponsor.

In the main phase, demographic characteristics were similar between treatment groups, with exception of a slightly lower proportion of males with MS CHF 5993 pMDI (29.5%) vs. HS CHF 1535 pMDI (37.5%). Overall, the vast majority of subjects (99.7%) were white with a predominance of females (66.5%). Subjects had a long-standing history of asthma, with an overall mean time since first diagnosis around 28 years and the majority (63.0%) had experienced 1 asthma exacerbation in the 3 years before screening, while the remaining subjects had experienced >1 asthma exacerbation. At screening (V1 [Week -2]), the overall mean pre-salbutamol FEV_1 was 61.4% of predicted normal value and ranged from 34.8% to 79.9% and the overall mean post-salbutamol FEV_1/FVC ratio was 0.686 and ranged from 0.50 to 0.91. Overall, 92 subjects with MS CHF 5993 pMDI and 78 subjects with HS CHF 1535 pMDI met the PAL criterion at screening.

Less than a quarter of the planned sample size was reached for the main phase and less than 10% for the OLE phase, so the study did not reach the sample size needed to ensure enough power for the analyses planned in the protocol. Therefore, only the primary and key secondary efficacy variables of the main phase are described in this abbreviated CSR. These are considered merely for information, as no meaningful conclusions on differences between treatments can be drawn due to the low sample size and the resulting underpowered analysis.

The primary efficacy variable, defined for the main phase, was the proportion of subjects exhibiting NPAL status on average over 26 weeks of treatment in the study sub-population meeting the PAL criterion at screening (ITT Set). In this sub-population of the ITT Set, the average NPAL status was observed in 13 (14.3%) subjects with MS CHF 5993 pMDI and 8 (10.3%) subjects with HS CHF 1535 pMDI. In the primary analysis of the main estimand using a logistic regression model, the odds ratio between MS CHF 5993 pMDI vs. HS CHF 1535 pMDI was 1.227 (95% CI: 0.418; 3.606) and the p-value was 0.709.

The key secondary efficacy variable in the main phase was the change from baseline in pre-dose morning FEV_1 at Week 26 in the study sub-population meeting the PAL criterion at screening (ITT Set). In the linear MMRM for the main estimand, the adjusted mean changes (95% CI) in the study sub-population meeting the PAL criterion at screening (ITT Set) indicated statistically significant increases from baseline in pre-dose FEV_1 at Week 26 with MS CHF 5993 pMDI (0.088 L [0.031; 0.146], p-value 0.003) and with HS CHF 1535 pMDI (0.145 L [0.083; 0.207],

p-value <0.001). The adjusted mean difference (95% CI) between MS CHF 5993 pMDI vs. HS CHF 1535 pMDI was -0.057 L (-0.142; 0.028) and the p-value was 0.190.

In the overall ITT Set, there were increases in the mean (standard deviation [SD]) pre-dose morning FEV_1 from baseline at Week 26 of 0.127 L (0.338) with MS CHF 5993 pMDI and 0.157 L (0.336) with HS CHF 1535 pMDI.

Safety Results:

Safety analyses were conducted in the Safety Set with a focus on the main phase. The mean extent of exposure to randomised study treatment in the Safety Set for the main phase was 25.20 weeks with MS CHF 5993 pMDI (100/6/12.5 µg BDP/FF/GB) and 25.17 weeks with HS CHF 1535 pMDI (200/6 µg BDP/FF).

The incidence of TEAEs in the main phase was similar between MS CHF 5993 pMDI (69 [44.2%] subjects reported with 127 events) and HS CHF 1535 pMDI (70 [43.8%] subjects reported with 113 events). The most common PT was asthma (PT for reported asthma exacerbations), reported at a similar incidence with MS CHF 5993 pMDI (26 [16.7%] subjects) and HS CHF 1535 pMDI (25 [15.6%] subjects), followed by nasopharyngitis, reported at a similar incidence with MS CHF 5993 pMDI (21 [13.5%] subjects) and HS CHF 1535 pMDI (14 [8.8%] subjects). Further PTs, reported with a similar incidence with MS CHF 5993 pMDI and HS CHF 1535 pMDI, were COVID-19 (4 [2.6%] and 8 [5.0%] subjects, respectively) and headache (6 [3.8%] and 3 [1.9%] subjects, respectively). There were no differences between treatment groups for any analysed SOC or PT in the comparative analyses.

The majority of TEAEs were mild or moderate in intensity. The incidence of severe TEAEs was similar between MS CHF 5993 pMDI (2 [1.3%] subjects) and HS CHF 1535 pMDI (8 [5.0%] subjects), and the 95% CI of the risk difference comprised 0. The only PT of severe TEAEs reported in >1 subject with any treatment was asthma (PT for reported asthma exacerbations), in 1 (0.6%) subject with MS CHF 5993 pMDI and in 4 (2.5%) subjects with HS CHF 1535 pMDI.

The incidence of ADRs in the main phase was low and comparable between treatment groups (3 [1.9%] subjects with MS CHF 5993 pMDI and 6 [3.8%] subjects with HS CHF 1535 pMDI). The only ADR reported in >1 subject by PT in any treatment group was dysphonia (in 2 [1.3%] subjects with HS CHF 1535 pMDI). None of the ADRs was serious and all were of mild or moderate intensity.

One subject in the HS CHF 1535 pMDI group experienced a TEAE leading to death in the main phase (PT cerebral haemorrhage). The incidence of overall serious TEAEs in the main phase was low and comparable between treatment groups (4 [2.6%] with MS CHF 5993 pMDI and 6 [3.8%] with HS CHF 1535 pMDI). Neither the TEAE leading to death nor any of the other serious TEAEs were considered related to study treatment. No serious TEAE SOC or PT was reported in >1 subject in any treatment group. Two of the serious TEAEs led to study treatment discontinuation (described below) and three further serious TEAEs in 2 subjects led to study treatment interruption. Most serious TEAEs resolved; the only exceptions were an event of lung neoplasm malignant (not resolved) and the fatal event of cerebral haemorrhage.

The proportion of subjects with TEAEs leading to treatment discontinuation in the main phase was low and equal between treatment groups (2 [1.3%] subjects in each treatment group; PTs pharyngitis and lung neoplasm malignant with MS CHF 5993 pMDI and cerebral haemorrhage and restlessness with HS CHF 1535 pMDI). The events of lung neoplasm malignant and cerebral haemorrhage were serious, and the latter was also fatal. These events were not considered related to study treatment. The events of pharyngitis and restlessness were considered related to study

treatment. Both events were non-serious, of moderate intensity and resolved.

Overall, 4 (2.6%) subjects with MS CHF 5993 pMDI and 8 (5.0%) subjects with HS CHF 1535 pMDI had a diagnosis of COVID-19 in the main phase. None of the events in subjects with a COVID-19 diagnosis was serious or reported as leading to study treatment discontinuation.

No serious post-treatment AEs were reported in the main phase. None of the TEAEs in the OLE phase led to death, was serious or led to study treatment discontinuation. No post-treatment AEs were reported for the OLE phase.

There were no meaningful safety signals emerging from standard haematology, biochemistry, vital sign and 12-lead ECG assessments.

Conclusion:

This study was terminated prematurely due to a substantial delay in recruitment and impact on timelines. Less than a quarter of the planned sample size was reached for the main phase and less than 10% for the OLE phase and the study did not reach the sample size needed to ensure enough power for the analyses planned in the protocol. The assessed efficacy results do not cast doubt on the effectiveness of the products for the proposed indication. All study treatments were safe and well tolerated, with no new safety concerns detected.

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