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: CHF 1535 100/6 µg pMDI	**Volume:**	
Name of Active Ingredient: beclometasone dipropionate and formoterol fumarate	**Page:**	

Title of Study:	Comparison of two formulations of beclometasone/formoterol pMDI on respiratory system impedance using impulse oscillometry in asthmatic patients
Investigator:	[redacted], MD
Study Centre:	[redacted]
Publication (Reference): Not applicable	

Studied Period: First patient first visit (FPFV): 14 March 2019 Last patient last contact (LPLC): 24 March 2020	**Phase of Development:** Phase IIa

Objectives:

The primary aim of the study was to evaluate the effect of two formulations of CHF 1535 100/6 µg pressurised metered-dose inhaler (pMDI) on area under the curve of reactance (AX) 0-60 min post-investigational medicinal product (IMP) administration in asthmatic patients.

The study had two secondary objectives:

- To evaluate the effect of two formulations of CHF 1535 100/6 µg pMDI on airway hyperresponsiveness (as methacholine provocative concentration causing a 40% increase in total respiratory system resistance [PC_{40} R5]) and reactivity (as response dose ratio [RDR]) in asthmatic patients.
- To evaluate the effect of two formulations of CHF 1535 100/6 µg pMDI on pre- and post-challenge impulse oscillometry (IOS) and pharmacokinetic (PK) profile.

SYNOPSIS

Methodology *(Study Design):*

Study CLI-01535AC1-03 started enrolment on 14 March 2019 and was put on hold in March 2020 due to the coronavirus disease 2019 (COVID-19) pandemic outbreak. Due to the pandemic, the study was not enrolling for 15 months and due to the projected prolonged timelines, in July 2021 Chiesi decided to early terminate the study [redacted].

Although the study was terminated prematurely, the methodology below is described as it was planned per protocol.

This clinical study was a Phase IIa study, with a single-centre, randomised, double-blind, multiple-dose, 2-way cross-over design.

Each treatment period was 3 to 4 weeks long and each patient was to take 2 puffs in the morning and 2 puffs in the evening of CHF 1535 100/6 µg commercial formulation or alternative product (AP), according to the randomisation list.

Randomised treatment period:

- Test treatment (Treatment T): CHF 1535 100/6 µg AP pMDI hydrofluoroalkane (HFA) (fixed combination of beclometasone dipropionate [BDP] 100 µg and formoterol fumarate [FF] 6 µg). Regimen: 2 puffs in the morning + 2 puffs in the evening (total daily dose: 400 µg of BDP + 24 µg of FF) for 3 to 4 weeks.
- Reference treatment (Treatment R): CHF 1535 100/6 µg (standard formulation) pMDI HFA (fixed combination of BDP 100 µg and FF 6 µg). Regimen: 2 puffs in the morning + 2 puffs in the evening (total daily dose: 400 µg of BDP + 24 µg of FF) for 3 to 4 weeks.

The study was to be conducted as follows for each patient:

- A screening visit to verify the eligibility of the patient for inclusion in the study and to start the step-down phase if needed. The purpose of the step-down phase was to gradually transition all patients to the same run-in therapy and lasted a maximum of 6 weeks depending on what medications the patient was taking at the screening visit. A separate visit could be conducted before the screening visit to collect patients' consent.
- At the conclusion of the step down (i.e., once the patient is on run-in therapy with Clenil® Modulite® 200 µg pMDI 1 puff twice a day), a visit was held to start the run-in period of 2 to 4 weeks. Clenil® Modulite® 200 µg pMDI was administered as 1 puff twice a day (total daily dose of beclometasone 400 µg) during the run-in period, taking the last dose in the morning before V1.
- A randomisation visit (V1) to randomise the patient to a treatment sequence and provide first treatment administration.
- Two treatment periods to provide treatment administration for 3 to 4 weeks, according to the randomised sequence. Treatment periods were to be separated by 2 to 4 weeks wash-out. Clenil® Modulite® 200 µg pMDI was administered as 1 puff twice a day (total daily dose of beclometasone 400 µg) during the wash-out period, the first intake was in the evening of V2 and the last dose was the morning before V3.
- Follow-up phone call or e-mail (from 1 to 2 weeks after the last study treatment intake), for safety checking. A visit could be scheduled if deemed necessary by the Investigator.

SYNOPSIS

Number of Patients *(Planned and Analysed)*:

In order to obtain 22 evaluable patients, approximately 24 asthmatic patients were planned to be randomised to be administered the two different treatments established according to the randomisation list.

In total, 13 patients were allocated to one of the two treatment sequences, of whom 6 patients to treatment sequence T-R and 7 patients to treatment sequence R-T.

Nine (69.2%) of the randomised patients completed the study. One (7.7%) patient discontinued due to an adverse event (AE) and 3 (23.1%) patients discontinued due to the coronavirus outbreak.

Diagnosis and Main Criteria for Inclusion:

Male and female asthma patients, aged 18 years and above, with a body mass index ≥20.0 and <45 kg/m^2, who were non- or ex-smokers who smoked ≤10 pack-years and stopped smoking >1 year prior to screening. Persistent asthma had to be diagnosed according to international guidelines (e.g., Global Initiative for Asthma [GINA]) at least 6 months before the screening visit. Patients had to be on 400-2000 µg BDP-equivalent inhaled corticosteroids per day with or without second- or third-line therapy. Patients had to have an AX >0.8 kPa·L^{-1} (average of three measurements) at screening and a forced expiratory volume in one second (FEV_1) ≥60% of predicted at screening.

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

CHF 1535 100/6 µg AP pMDI HFA (fixed combination of BDP 100 µg and FF 6 µg) – 2 puffs in the morning + 2 puffs in the evening (total daily dose: 400 µg of BDP + 24 µg of FF) – Batch numbers: [redacted], [redacted], and [redacted].

Duration of Treatment:

The study consisted of a screening visit, a step-down phase of 0 to 6 weeks, a run-in period of 2 to 4 weeks, 2 treatment periods of 3 to 4 weeks, separated by at least 2 to 4 wash-out weeks between two consecutive treatment intakes, and a follow-up call within 1 to 2 weeks after the last study treatment intake. The total study duration was between 11 to 24 weeks per patient.

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

CHF 1535 100/6 µg (standard formulation) pMDI HFA (fixed combination of BDP 100 µg and FF 6 µg) – 2 puffs in the morning + 2 puffs in the evening (total daily dose: 400 µg of BDP + 24 µg of FF) – Batch numbers: [redacted], [redacted], and [redacted].

Criteria for Evaluation:

Efficacy Variables:

Since the study was terminated prematurely, efficacy variables were not analysed (data for individual patients were listed only). The methodology below reflects what was planned per protocol.

SYNOPSIS

Primary Efficacy Variables

- AX post-chronic IMP administration (V2 and V4) measured over 60 min vs. AX baseline before the first IMP administration (V1 and V3).

Secondary Efficacy Variables

- Respiratory system resistance at 20 Hertz (R20), peripheral respiratory system resistance as the difference between 5 and 20 Hertz (R5-R20), respiratory system resistance at 5 Hertz (R5), respiratory system reactance at 5 Hertz (X5), and resonance frequency (RF) post-chronic IMP administration (V2 and V4) measured over 60 min vs. R20, R5-R20, R5, X5, and RF baseline before the first IMP administration (V1 and V3).
- AX, R20, R5-R20, R5, X5, and RF IOS pre-IMP at V2/V4 vs. IOS baseline (pre-IMP) at V1/V3.
- IOS profile post-IMP at V2/V4 vs. IOS pre-IMP.
- PC_{40} R5 and RDR during methacholine challenge at V2/V4.
- IOS recovery after the challenge, measured with AX, R20, R5-R20, R5, X5, and RF vs. IOS post-IMP at V2/V4.

Exploratory Efficacy Variables

- Blood eosinophils.
- Fractional exhaled nitric oxide (FeNO).

Pharmacokinetic Variables

Since the study was terminated prematurely, PK variables were not estimated. The methodology below reflects what was planned per protocol.

Pharmacokinetic Variables

- Plasma beclometasone 17-monopropionate (B17MP) and formoterol: area under the plasma concentration-time curve from administration to 30 min post-dose ($AUC_{0-30min}$), AUC from administration to 2 h post-dose (AUC_{0-2h}), AUC from 0 to the last quantifiable concentration (AUC_{0-t}), maximum plasma concentration (C_{max}), and time to reach C_{max} (t_{max}).
- Plasma BDP: $AUC_{0-30min}$, AUC_{0-t}, C_{max}, t_{max}, and terminal half-life ($t_{1/2}$).

Safety Variables:

- AEs and adverse drug reactions (ADRs).
- FEV_1 and forced vital capacity.
- Vital signs: systolic blood pressure, diastolic blood pressure, pulse rate.
- Use of rescue medication.
- Morning domiciliary peak expiratory flow (PEF).
- Asthma Control Questionnaire 6 (ACQ6).

SYNOPSIS

Statistical Methods:

Efficacy Variables:

All IOS data (actual values) were listed. An additional listing included the information on the methacholine challenge test. All FeNO data (actual values) were listed.

Pharmacokinetic Variables:

No PK parameters were estimated. Actual blood sampling times from drug administration for PK assessments as well as BDP/B17MP and formoterol plasma concentrations were listed.

Safety Variables:

A summary table presenting all treatment-emergent AEs (TEAEs) was created. All safety data were listed: AEs, including pre-treatment events, laboratory data (actual values and abnormalities), vital signs data (actual values, change from baseline, and corresponding abnormalities), electrocardiogram (ECG) parameters (actual values), lung function parameters, data on PEF, data (actual values) on the ACQ6 score, and abnormal physical examination findings.

Summary:

Efficacy Results:

Since the study was terminated prematurely, efficacy variables were not analysed and therefore not described in this Clinical Study Report.

Pharmacokinetic Results:

Since the study was terminated prematurely, PK variables were not analysed and therefore not described in this Clinical Study Report.

Safety Results:

One (7.7%) patient experienced TEAEs leading to study discontinuation. This patient was reported with the moderate, not-related TEAEs viral upper respiratory tract infection and asthma (reported term: asthma exacerbation) reported in the wash-out period between Treatment Period 1 and 2.

Overall, 27 TEAEs were reported in 9 (69.2%) patients, i.e., 7 (63.6%) patients reported a TEAE after inhalation of CHF 1535 100/6 µg AP pMDI HFA and 6 (54.5%) patients after inhalation of CHF 1535 100/6 µg pMDI HFA.

By preferred term, the most frequently reported TEAEs were headache (in 3 patients overall), viral upper respiratory tract infection (in 3 patients overall), and nausea (in 2 patients overall). Other TEAEs were reported in at most 1 patient overall.

No deaths or other serious AEs were reported during the study.

All TEAEs were mild or moderate in intensity.

SYNOPSIS

Overall, 3 TEAEs in 1 patient were considered to be treatment related by the Investigator: dyspepsia, nausea, and oropharyngeal pain in 1 patient after inhalation of CHF 1535 100/6 µg AP pMDI HFA. All 3 ADRs were mild in intensity and were considered resolved before the end of the patient's study participation.

At Least One Treatment-Emergent Adverse Event (TEAE)	CHF 1535 100/6 µg AP pMDI HFA (test treatment) N=11*		CHF 1535 100/6 µg pMDI HFA (reference treatment) N=11*		Overall N=13*	
	n (%)	E	n (%)	E	n (%)	E
TEAE	7 (63.6)	17	6 (54.5)	11	9 (69.2)	27
Serious TEAE	0		0		0	
Non-serious TEAE	7 (63.6)	17	6 (54.5)	11	9 (69.2)	27
ADR	1 (9.1)	3	0		1 (7.7)	3
Serious ADR	0		0		0	
Severe TEAE	0		0		0	
TEAE leading to study drug discontinuation	1 (9.1)	2	0		1 (7.7)	2
TEAE leading to death	0		0		0	

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

* In each treatment sequence, 2 patients discontinued treatment prior to the second treatment period, resulting in 11 of the 13 patients overall receiving at least one dose of CHF 1535 100/6 µg AP pMDI HFA and 11 of the 13 patients overall receiving at least one dose of CHF 1535 100/6 µg pMDI HFA.

All 13 patients used rescue medication (salbutamol) during the study.

No post-baseline abnormalities in lung function were reported. Based on assessment by the Investigator, PEF remained stable for all patients.

No laboratory-related, vital sign-related, ECG-related, lung function-related, and physical examination-related TEAEs were reported.

Conclusion:

Study CLI-01535AC1-03 started enrolment on 14 March 2019 and was put on hold in March 2020 due to the COVID-19 pandemic outbreak. Due to the pandemic, the study was not enrolling for 15 months and due to the projected prolonged timelines, in July 2021 Chiesi decided to early terminate the study [redacted].

In conclusion, based on the collected data, CHF 1535 100/6 µg AP pMDI HFA and CHF 1535 100/6 µg pMDI HFA were safe and well tolerated.

Date of Report: 18 March 2022