CLINICAL STUDY REPORT

STUDY CODE No.: CLI-06532AA1-01

EUDRACT No.: 2018-003548-22

A 52 WEEK, RANDOMISED, DOUBLE BLIND, MULTINATIONAL, MULTICENTRE, 4-ARM PARALLEL GROUP TRIAL TO ASSESS THE EFFICACY AND SAFETY OF 3 DOSES OF CHF 6532 (10, 25, or 50 mg BID) COMPARED TO PLACEBO ON TOP OF STANDARD OF CARE IN PATIENTS WITH UNCONTROLLED SEVERE EOSINOPHILIC ASTHMA (PERSEA).

Version No.: Final 1.0
Date: 17 August 2021

Chiesi Farmaceutici S.p.A.
Via Palermo 26/A
43122 Parma– Italy

1. TITLE PAGE

Study Title:	A 52 week, randomised, double blind, multinational, multicentre, 4-arm parallel group trial to assess the efficacy and safety of 3 doses of CHF 6532 (10, 25, or 50 mg BID) compared to placebo on top of standard of care in patients with uncontrolled severe eosinophilic asthma (PERSEA).
Product:	CHF 6532
Pharmaceutical Form:	Oral tablet
Indication:	Severe eosinophilic asthma
Development phase of study:	III
Study Start Date (First patient first visit; FPFV):	28th August 2019
Study Completion Date (Last patient last visit; LPLV):	1st February 2021

"This study was conducted in compliance with the International Council for Harmonisation of Technical Requirements for Human Use – Guidelines for Good Clinical Research Practices (ICH GCP E6), including the archiving of essential documents".

VERSION HISTORY

Version	Date	Change History
1.0	17 August 2021	First version

2. SYNOPSIS

Name of Company: Chiesi Farmaceutici S.p.A. (Chiesi)	**Individual Study Table Referring to Part of the Dossier**	*(for National Authority Use only)*
Name of Finished Product: CHF 6532		
Name of Active Ingredient: Timapiprant	**Volume:** **Page:**	

Title of Study: A 52-week, randomised, double blind, multinational, multicentre, 4-arm parallel group trial to assess the efficacy and safety of 3 doses of CHF 6532 (10, 25, or 50 mg BID) compared to placebo on top of standard of care in patients with uncontrolled severe eosinophilic asthma (PERSEA).

Investigators: 126 recruiting Investigators in 11 countries

Study Centres: 126 recruiting centres (140 initiated) in 11 countries

Publication (*Reference*): None

Studied Period: FPFV: 28 August 2019 LPLV: 01 February 2021	**Phase of Development:** Phase III

Objectives:

Primary Objective:

- To demonstrate the efficacy of at least one dose of CHF 6532 on moderate and severe asthma exacerbation rate compared to placebo arm over 52 weeks of treatment.

Secondary Objectives:

- To assess the effect of CHF 6532 on severe asthma exacerbations compared to placebo over 52 weeks of treatment;
- To assess the effect of CHF 6532 compared to placebo in terms of change from baseline in pre-dose morning forced expiratory volume in the first second (FEV_1) at Week 52;
- To assess the effect of CHF 6532 compared to placebo in terms of change from baseline on St. George's Respiratory Questionnaire (SGRQ), Asthma Control Questionnaire 5 (ACQ-5) and Asthma Quality of Life Questionnaire for 12 Years and Older (AQLQ+12) at Week 52;
- To perform a population pharmacokinetics (PK) analysis investigating the inter-patient variability in the drug exposure and the effect of selected covariates on PK;
- To collect data in order to assess the impact of study treatments on health economics outcome;

- To assess the safety and the tolerability of the study treatments with respect to adverse events (AEs), electrocardiograms (ECGs), vital signs and laboratory tests.

Exploratory Objective:

- To assess the efficacy of CHF 6532 compared to placebo on other lung function parameters and clinical outcome measures.

Methodology *(Study Design)*:

This was a phase III, randomised, double-blind, placebo-controlled, multinational, multicentre, 4-arm parallel-group study which evaluated 3 doses of CHF 6532. The study was designed to demonstrate the superiority of CHF 6532 over placebo in terms of rate of moderate and severe exacerbation over 52 weeks of treatment in patients with severe eosinophilic uncontrolled asthma treated with the combination of high-dose inhaled corticosteroids (ICS) and long-acting β_2-agonist (LABA), with or without long-acting muscarinic antagonist (LAMA), with or without oral corticosteroids (OCS).

The study consisted of four periods: a 2-week pre-screening period, a 2- to 4-week run-in period, a 52-week treatment period and a 2-week follow-up period. The study comprised 8 visits at clinic, plus a follow-up phone call. A pre-screening visit (Visit 0 [V0]) was planned to occur no more than 2 weeks before a screening visit (V1), followed by a 2-week run-in period (which could be extended to 4-weeks to achieve the compliance level threshold of 50%), where patients received their own standard of care (SoC) and OCS if taken before the study entry.

At the randomisation visit (V2 [Week 0]), patients were randomised in a 1:1:1:1 ratio to receive one of the following treatments for 52 weeks:

- CHF 6532 10 mg, 1 tablet orally twice daily (BID) (total daily dose: 20 mg timapiprant);
- CHF 6532 25 mg, 1 tablet orally BID (total daily dose: 50 mg timapiprant);
- CHF 6532 50 mg, 1 tablet orally BID (total daily dose: 100 mg timapiprant);
- Placebo.

The study treatment was administered orally to patients, in addition to their usual SoC treatment. Subsequent visits were performed after 4 weeks (V3), 12 weeks (V4), 26 weeks (V5), 40 weeks (V6) and 52 weeks (V7) of treatment. An early treatment discontinuation (ETD) visit was to be performed in the event of premature study discontinuation; all the assessments foreseen at V7 (Week 52) were to be done. A safety follow-up phone call was made by the Investigator 2 weeks after V7 (Week 52) or ETD visit.

An interim analysis was planned in order for an independent data monitoring committee (DMC) to assess futility. As the protocol-defined futility rules were met, the DMC recommended that the study be stopped for futility. In line with that recommendation, the Sponsor issued a notification of early study termination thereafter.

Number of Patients *(Planned and Analysed)*:

It was planned to randomise about 1392 adult patients in a 1:1:1:1 ratio to the 3 doses of CHF 6532 (348 patients on each dose) or placebo (348 patients). In addition, it was planned to randomise about 248 adolescent patients to the 3 doses of CHF 6532 (62 patients on each dose) or placebo (62 patients).

Of note, a subgroup of about 320 adult patients was to be selected to reach about 80 evaluable patients per arm for the PK analysis at each CHF 6532 dose level.

	CHF 6532 10 mg	CHF 6532 25 mg	CHF 6532 50 mg	Placebo	Overall
Randomised set, n	200	203	202	205	810
Safety set, n	200	203	202	205	810
ITT set, n	200	203	202	205	810
PK assessment set	40	53	49	0	142
PK set, n[a]	39	51	45	0	135

ITT = Intention-to-treat; PK = Pharmacokinetic.
n = Number of patients in each set.
[a] Defined as all patients from the PK assessment set, excluding patients without any valid PK measurement, or with major protocol deviations affecting PK.

Diagnosis and Main Criteria for Inclusion:

Eligible patients included male or female patients aged ≥ 12 and ≤ 75 years with uncontrolled asthma, evidenced by a score on the ACQ-5 ≥ 1.5, and on high doses of ICS in combination with LABA, with or without LAMA, with or without OCS. Patients had to have a documented history of asthma for at least 24 months and a documented history of at least 2 asthma exacerbations requiring treatment with systemic corticosteroids or emergency department visit or in-patient hospitalisation within 52 to 4 weeks prior to screening. Patients had to have a positive response to a reversibility test defined as a change in FEV_1 (ΔFEV_1) > 12% and > 200 mL over baseline within 10-15 minutes (mins) after inhaling 400 µg of salbutamol pressurised metered-dose inhaler (pMDI).

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

Test product: CHF 6532 tablets.

Doses: 10 mg, 25 mg, and 50 mg, BID. Total daily doses: 20 mg, 50 mg, and 100 mg.

Mode of administration: Oral.

Batch numbers:

CTS Campaigns	Product	Batch numbers of the blinded treatment kit	Chiesi Batch numbers	Expiry Dates
C1a	CHF 6532 10 mg	E198734-11	1851A006	30 November 2021
C1a	CHF 6532 25 mg	E198734-11	1851A007	30 November 2021
C1a	CHF 6532 50 mg	E198734-11	1851A008	30 November 2021
C1b	CHF 6532 10 mg	E198734-05	1851A006	30 November 2021
C1b	CHF 6532 25 mg	E198734-05	1851A007	30 November 2021
C1b	CHF 6532 50 mg	E198734-05	1851A008	30 November 2021
C2	CHF 6532 10 mg	E198734-10	1949A007	30 September 2022
C2	CHF 6532 25 mg	E198734-10	1948A015	30 September 2022
C2	CHF 6532 50 mg	E198734-10	1948A016	30 September 2022

Duration of Treatment:

A 2- to 4-week run-in period on background medication, followed by a 52-week treatment period on randomised treatment.

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

- Matched placebo;
- Background medication: SoC with or without OCS.

CTS Campaigns	Product	Batch numbers of the blinded treatment kit	Chiesi Batch numbers	Expiry Dates
C1a	Placebo of CHF 6532 10 mg, 25 mg, 50 mg, blister 14 tablets	E198734-11	1851A005	30 November 2021
C1b	Placebo of CHF 6532 10 mg, 25 mg, 50 mg, blister 14 tablets	E198734-05	1851A005	30 November 2021
C2	Placebo of CHF 6532 10 mg, 25 mg, 50 mg, blister 14 tablets	E198734-10	1948A014	30 September 2022

Criteria for Evaluation:

Efficacy:

The efficacy variables are presented as planned in the CSP and modified in the statistical analysis plan (SAP) version 2.0.

Primary efficacy variable:

- Rate of moderate and severe asthma exacerbation over 52 weeks of treatment.

Secondary efficacy variables:

- Time to first moderate or severe exacerbation;
- Severe exacerbations rate over 52 weeks of treatment;
- Change from baseline in pre-dose FEV_1 at Week 52;
- Change from baseline in pre-dose FEV_1 % predicted at Week 52;
- FEV_1 response (defined as change from baseline in pre-dose $FEV_1 \geq 100$ mL) at Week 12 and 26;
- Change from baseline in SGRQ total score and domain scores at Week 52;
- Change from baseline in ACQ-5 at Week 52;
- Change from baseline in AQLQ+12 total and domain scores at Week 52.

Exploratory efficacy variables:

- Change from baseline in pre-dose forced vital capacity (FVC);
- Change from baseline in pre-dose forced expiratory flow between 25% and 75% of FVC ($FEF_{25\%-75\%}$);
- Change from baseline in pre-dose FEV_1 at all other clinical visits;
- Change from baseline in pre-dose FEV_1 % predicted at all other clinical visits;
- Change from baseline in SGRQ total score and domain scores at all other clinical visits;
- Change from baseline in ACQ-5 at all other clinical visits;
- Change from baseline in AQLQ+12 total and domain scores at all other clinical visits;
- ACQ-5 response (change from baseline in ACQ-5 score $\leq$ -0.5) at Week 26;
- SGRQ response (change from baseline in SGRQ total score $\leq$ -4) at Week 26;

- Change from baseline to each inter-visit period and to the entire treatment period in the average day-time, night-time and total daily rescue medication use (number of puffs), day-time, night-time and total daily asthma symptoms score;
- Change from baseline to each inter-visit period and to the entire treatment period in the percentage of rescue medication-free days, in the asthma symptoms-free days and in the asthma control days;
- Change from baseline to each inter-visit period and to the entire treatment period in average pre-dose morning and evening peak expiratory flow (PEF);
- Change from baseline in blood eosinophils and blood basophils (absolute number).

Safety:

- AEs and adverse drug reactions (ADRs);
- Vital signs: systolic blood pressure (SBP) and diastolic blood pressure (DBP);
- 12-lead ECG parameters: heart rate (HR), Fridericia-corrected QT interval (QTcF), PR interval (PR) and QRS interval (QRS);
- Standard haematology and blood chemistry.

Pharmacokinetics:

- Plasma concentration data of CHF 6532 and CHF 6532 AG.

Statistical Methods:

The following analysis sets were considered for analysis:

- Intention-to-Treat (ITT) set defined as all randomised patients who received at least one dose of the study treatment (analysed as randomised);
- Safety set defined as all randomised patients who received at least one dose of the study treatment (analysed as treated);
- PK set defined as the subgroup from the Safety set selected for PK analysis (PK assessment set) and treated with CHF 6532 (analysed as treated), excluding patients without any valid PK measurement or with major protocol deviations significantly affecting PK;
- Randomised set defined as all patients randomised to study treatment.

Since the superiority of CHF 6532 at different doses over placebo was tested, the primary efficacy analysis was based on the ITT set. For exploratory purposes, the analyses of the primary efficacy variable and the secondary efficacy variable change from baseline in pre-dose FEV_1 at Week 52, were performed on the ITT set stratified by relevant factors (including age group, gender, body mass index [BMI], region, number of asthma exacerbations in the previous year, blood eosinophils level at screening and immunoglobulin E (IgE) levels at baseline; the primary efficacy variable analysis was also performed stratified by presence of nasal polyps at screening).

All secondary and exploratory efficacy variables were analysed in the ITT set. The safety variables were analysed in the Safety set. The PK variables were analysed in the PK set.

Efficacy analysis

Primary efficacy variable

The primary efficacy variable was the rate of moderate and severe asthma exacerbation over 52 weeks of treatment. Comparisons between the different CHF 6532 dose levels and placebo were conducted in the ITT set according to a hierarchical testing procedure in the following order:

1. CHF 6532 50 mg versus (vs.) placebo;
2. CHF 6532 25 mg vs. placebo;
3. CHF 6532 10 mg vs. placebo.

At each step of the procedure, no confirmatory claims were made unless the superiority of CHF 6532 over placebo was demonstrated in all the preceding steps.

The number of moderate and severe asthma exacerbations was analysed using a negative binomial model including treatment, region, number of asthma exacerbations in the previous year, OCS use at study entry and age group as fixed effects, and the natural logarithm of duration of follow-up in years as an offset. The adjusted exacerbation rate in each treatment group and the adjusted rate ratios between each CHF 6532 dose level and placebo with their 95% Wald confidence intervals (CIs) and p-values were estimated by the model. Superiority at each dose level over placebo was demonstrated if the p-value for the adjusted rate ratio was < 0.05.

The validity of the model planned relied on the missing at random (MAR) assumption, which targets a hypothetical estimand (hereafter referred to as primary estimand) that estimated the treatment effect that would have been observed if all patients had continued on treatment for the full study duration. An analysis targeting an alternative estimand based on the treatment policy strategy was also conducted: analysis of the effect of treatment initially assigned at randomisation, regardless of adherence to the planned course of treatment.

Secondary efficacy variables

All analyses on secondary efficacy variables considered all data recorded in the randomised period, based on the primary estimand, with a MAR assumption for missing data:

- Time to first moderate or severe asthma exacerbation was analysed using a Cox proportional hazards model including treatment, region, number of asthma exacerbations in the previous year, OCS use at study entry and age group as factors;
- Severe asthma exacerbation rate over 52 weeks was summarised by treatment group using descriptive statistics;
- Changes from baseline at V7 (Week 52) in pre-dose FEV_1, pre-dose FEV_1 % predicted, SGRQ total score and domain scores, ACQ-5 total score and AQLQ+12 total score and domain scores were analysed using a linear mixed model for repeated measures (MMRM) including treatment, visit, treatment by visit interaction, region, number of asthma exacerbations in the previous year, OCS use at study entry and age group as fixed effects, and baseline value and baseline by visit interaction as covariates. The adjusted means in each treatment group, the adjusted mean differences between treatments, their 95% CIs and corresponding p-values at V5 (Week 26) were estimated by the model.

  Of note, only data until, and including, V5 (Week 26), i.e. Month 6, were considered for the analysis model due to early termination of the study.

  Values for each parameter were summarised by treatment group using descriptive statistics. Change from baseline was also summarised by treatment group;
- FEV_1 response at V4 (Week 12) and V5 (Week 26) was defined as a change from baseline in pre-dose $FEV_1 \geq 100$ mL. The FEV_1 response was compared between treatment groups using

a logistic regression model including treatment, region, number of asthma exacerbations in the previous year, OCS use at study entry and age group as factors and the baseline value as a covariate. The odds ratios for treatment comparisons with their 95% CIs and corresponding p-values were estimated by this model.

Exploratory efficacy variables

- Changes from baseline at all clinical visits in pre-dose FVC and pre-dose $FEF_{25\%-75\%}$ and at all other clinical visits in pre-dose FEV_1, pre-dose FEV_1 % predicted, SGRQ total score and domain scores, ACQ-5 total score and AQLQ+12 total score and domain scores were summarised using the same approach as for change from baseline in pre-dose FEV_1 at V7 (Week 52);
- ACQ-5 and SGRQ responses at V5 (Week 26) were summarised using the same approach as for FEV_1 response;
- Change from baseline to each inter-visit period and to the entire treatment period in the average day-time, night-time and total daily rescue medication use; day-time, night-time and total daily asthma symptoms scores; percentage of rescue medication-free days; asthma symptoms-free days and asthma control days and in average pre-dose morning and evening PEF were summarised using the same approach as for change from baseline in pre-dose FEV_1 at V7 (Week 52);
- Change from baseline in the level of blood eosinophils at all clinical visits was summarised using the same approach as for change from baseline in pre-dose FEV_1 at V7 (Week 52);
- Change from baseline in the level of blood basophils at all clinical visits was summarised using the same approach as for change from baseline in pre-dose FEV_1 at V7 (Week 52).

Safety analysis

The number and percentage of patients who experienced at least one treatment-emergent adverse event (TEAE), ADR, serious TEAE, serious ADR, severe TEAE, TEAE leading to study treatment discontinuation and TEAE leading to death were summarised by treatment group and overall. The number of corresponding events was presented by system organ class (SOC) and preferred term (PT) according to Medical Dictionary for Regulatory Activities (version 22.0). Subgroup analysis of TEAEs was also performed stratified by age group (adolescents/adults).

Mean absolute values and mean changes from baseline (V2 [Week 0] pre-dose) to each time point after the first study treatment intake and from pre-dose to 10 mins post-dose at each visit in vital signs (SBP and DBP) were calculated with their 95% CI by treatment group.

At each time point after the first study treatment intake, 12-lead ECG parameters (HR, QTcF, PR and QRS) and their changes from baseline (V2 [Week 0] pre-dose) were summarised as i) mean absolute values with two-sided 95% CIs and ii) mean change from baseline with two-sided 90% CIs.

Abnormalities in QTcF absolute values and changes from baseline were presented by treatment group.

Shift tables from baseline (V2 [Week 0]) to the end of treatment with reference to normal ranges were presented by treatment group for each of the laboratory parameters.

PK analysis

Individual plasma concentration data of CHF 6532 and CHF 6532-AG in the PK assessment set were listed by scheduled sampling times and summarised using descriptive statistics in the PK set.

Summary – Results:

Efficacy Results:

In this study, a total of 810 patients were randomised to receive 1 of 4 treatments (200, 203, 202 and 205 patients randomised to receive CHF 6532 10 mg, CHF 6532 25 mg, CHF 6532 50 mg and placebo, respectively). An interim futility analysis was performed when 411.76 patient-years of follow-up data had been collected, considering all randomised patients with at least 3 months of follow-up at the futility cut-off date. The DMC reviewed the efficacy and futility materials and recommended to the Sponsor that the study be stopped for futility as the pre-defined futility rules had been met (i.e. conditional power was < 80% at interim analysis for all comparisons of CHF 6532 dose levels vs. placebo). After Sponsor decision to terminate the study, patients enrolled and still ongoing in the study were withdrawn. Most patients did not have efficacy data at Week 40 and Week 52.

Overall, 189 (23.3%) patients completed the study treatment and the study (22.7% to 24.8% of patients across treatment groups) and 591 (73.0%) patients discontinued the study treatment and the study due to the Sponsor decision to stop the study (71.7% to 74.4% of patients across treatment groups). A similar proportion of patients attended the on-treatment and off treatment period visits in all treatment groups. During the on-treatment period, 99.1%, 88.1%, 65.3%, 60.6%, 23.0% and 38.3% of patients overall attended the Week 4, Week 12, Week 26, Week 40, Week 52 and ETD visits, respectively.

Demographic and baseline characteristics were generally comparable between the treatment groups. Most patients were white (except 3 patients) and adults (97.3%); more females were enrolled (64.9%). More than half the patients had an asthma duration of ≥ 5 years to < 20 years with overall mean time since asthma diagnosis of 17.7 years, and 88.0% overall were non-smokers. In the CHF 6532 50 mg treatment group, 46.0% of patients had an asthma duration of ≥ 5 years to < 20 years and 39.6% of patients had an asthma duration ≥ 20 years compared to 52.2% to 54.7% and 30.0% to 34.1% of patients, respectively in other treatment groups.

At study entry, across treatment groups, mean pre-bronchodilator FEV_1 % predicted ranged from 58.5% to 61.3%; mean reversibility in FEV_1 ranged from 471 to 506 mL (27.7% to 31.4%); and mean ACQ-5 scores ranged from 2.52 to 2.61 (indicating uncontrolled asthma in patients treated according to GINA Step 4 or Step 5 [2018 update]). At baseline, after the run-in period, mean ACQ-5 scores ranged across treatment groups from 2.35 to 2.48, indicating uncontrolled asthma on SoC with/without OCS. At baseline (Week 0 pre-dose), mean FEV_1 and FEV_1 % predicted ranged across treatment groups from 1.893 to 2.020 L and 63.7% to 66.3%, respectively. Most patients (90.1% overall) had a history of 2 asthma exacerbations in the previous year and 9.9% of patients overall had a history of > 2 asthma exacerbations in the previous year. At screening and baseline, across treatment groups, the mean blood eosinophil count varied from 446.7 to 470.1 cells/µL and 418.4 to 443.3 cells/µL, respectively.

Compliance to SoC and OCS during the run-in period and the randomised treatment period (means ranging from 84.7% to 91.3% overall), and to the study treatment during the on-treatment period (mean of 90.0% overall) was satisfactory. Compliance to the eDiary of [80%–100%] was reported for 83.8% of patients overall during the on-treatment period.

Primary efficacy analysis

The primary efficacy variable (i.e. the rate of moderate and severe asthma exacerbations) was analysed considering only asthma exacerbations that occurred during the on-treatment period (thus targeting a hypothetical estimand). Overall, moderate and severe asthma exacerbations were experienced by 190 (23.5%) patients during the on-treatment period (with moderate exacerbations accounting for 96.0% of the events). There was no evidence of a CHF 6532 dose effect; 20.5%,

21.3% and 26.6% of patients experienced events with CHF 6532 10 mg, CHF 6532 50 mg and CHF 6532 25 mg, respectively (63, 79 and 86 events, respectively). With placebo, 25.4% of patients experienced 71 events. A greater proportion of events were severe with CHF 6532 10 mg (7.9%) than with other treatments (2.3% to 4.2%).

The adjusted exacerbation rates per patient per year (95% CI) observed with CHF 6532 10 mg, CHF 6532 25 mg, CHF 6532 50 mg and placebo were 0.41 (0.30; 0.57), 0.51 (0.38; 0.68), 0.44 (0.32; 0,59) and 0.42 (0.31; 0.58), respectively. The adjusted rate ratio (95% CI) of 1.03 (0.68; 1.57) for the comparison of CHF 6532 50 mg vs. placebo (p=0.884) indicated that there was no difference between treatments in the rate of moderate and severe asthma exacerbations. As superiority of CHF 6532 50 mg over placebo was not demonstrated, as per the pre-specified hierarchical testing procedure, no further confirmatory claim can be made from comparisons of other CHF 6532 doses vs. placebo. Superiority of CHF 6532 over placebo was therefore not demonstrated in terms of the rate of moderate and severe asthma exacerbations over 52 weeks of treatment.

There was a 21% increase in the rate of moderate and severe asthma exacerbations with CHF 6532 25 mg compared to placebo (adjusted rate ratio: 1.21, p=0.376) and no difference between treatments for the comparison of CHF 6532 10 mg vs. placebo (adjusted rate ratio: 0.97, p=0.908).

Stratified analyses showed a statistically significant 85% reduction in the rate of moderate and severe asthma exacerbations with CHF 6532 10 mg compared to placebo in the subgroup with > 2 exacerbations in the previous year at study entry (adjusted rate ratio: 0.15, p=0.008). There was a statistically significantly lower rate of moderate and severe exacerbations with placebo than with CHF 6532 25 mg and CHF 6532 10 mg in males and in patients with presence of nasal polyps at screening (adjusted rate ratios: 2.56 to 3.26, $p < 0.05$ for the comparisons of CHF 6532 dose levels vs. placebo). For other stratified analyses performed on the primary efficacy variable, adjusted rate ratios for comparisons of CHF 6532 dose levels vs. placebo ranged from 0.57 to 1.81 ($p > 0.1$ for all).

Secondary efficacy analysis

The time to first moderate or severe exacerbation was prolonged with CHF 6532 50 mg and CHF 6532 10 mg and decreased with CHF 6532 25 mg compared to placebo (hazard ratios: 0.804, 0.742 and 1.025, respectively; $p > 0.1$ for all). Severe asthma exacerbations were reported for 1.0% to 2.5% of patients across treatment groups.

For analysis of pre-dose FEV_1, only data until Week 26 were considered in the analysis model. There were statistically significant increases from baseline (i.e. improvements) at Week 26 with all treatments (adjusted means ranging from 0.101 to 0.163 L, $p < 0.001$ for all) and no statistically significant differences between CHF 6532 dose levels and placebo, though the increase from baseline was numerically greater with CHF 6532 25 mg compared to placebo (adjusted mean difference: 0.051 L; p=0.151). There were statistically significant increases from baseline in pre-dose FEV_1 % predicted at Week 26 with all treatments (adjusted means ranging from 3.2% to 4.9%, $p < 0.001$ for all), with no differences between CHF 6532 dose levels and placebo (adjusted mean differences: 0.7% to 1.0%; $p > 0.1$ for all comparisons).

A similar proportion of patients were FEV_1 responders at Week 12 with all treatments (39.6% to 42.0%) and a greater proportion of patients were FEV_1 responders with placebo at Week 26 (47.2%) than with the CHF 6532 dose levels (42.0% to 45.1%) with no statistically significant differences between CHF 6532 dose levels and placebo at either timepoint (odds ratios: 0.797 to 1.085, $p > 0.2$ for all comparisons).

Statistically significant improvements compared to baseline were observed with all treatments for SGRQ total and domain scores, ACQ-5 scores and AQLQ+12 total and domain scores at Week 26,

with no statistically significant differences between CHF 6532 dose levels and placebo ($p > 0.06$ for all comparisons).

Exploratory efficacy endpoints

Only descriptive statistics were provided for exploratory efficacy endpoints. There were increases from baseline with all treatments at all visits for pre-dose FVC, $FEF_{25\%-75\%}$, FEV_1 and FEV_1 % predicted (at 45 mins and 15 mins pre-dose) with mean increases ranging from 0.037 to 0.149 L, 0.055 to 0.194 L, 0.044 to 0.162 L and 0.9% to 4.8%, respectively.

With all treatments, improvements from baseline were observed for total and domain SGRQ scores at Week 12 and Week 52; for ACQ-5 scores and AQLQ+12 total scores at all visits; and for AQLQ+12 domain scores at all visits except for a decrease from baseline in environmental stimuli scores (AQLQ+12) at Week 52 with CHF 6532 25 mg.

At Week 26, 62.9% of patients had achieved an ACQ-5 response with CHF 6532 10 mg and placebo, compared to 60.6% with CHF 6532 25 mg and 56.7% with CHF 6532 50 mg. With all treatments, less than half the patients had controlled asthma (i.e. ACQ-5 score < 1.5) (39.7% to 45.1% of patients), and 55.6% to 62.1% of patients were classified as SGRQ responders.

Improvement in asthma control compared to baseline was seen with all treatments in each inter-visit period and over the entire treatment period in terms of reduction in average day-time, night-time and total daily rescue medication use; increase in percentage of rescue medication free days; decrease in average day-time, night-time and daily asthma symptoms scores; and increase in percentage of asthma symptom-free days and asthma control days. For average pre-dose morning and evening PEF, compared to baseline, there was either no change or improvement in all inter-visit periods and over the entire treatment period with all CHF 6532 dose levels. With placebo, compared to baseline, there was no change in average pre-dose morning PEF and decrease in average pre-dose evening PEF in the Weeks 1 to 4 inter-visit period, and improvements for both parameters in subsequent inter-visit periods and over the entire treatment period.

From Week 4 to Week 52, mean changes from baseline in blood eosinophil and basophil levels ranged from -122.8 to 18.3 cells/µL and -0.053 to 0.001 cells/µL, respectively with all treatments.

Safety Results:

Exposure to study treatment was similar across treatment groups (means ranging from 261 to 267 days). The proportion of patients who completed at least 52 weeks of treatment was similar across treatment groups, ranging from 20.0% to 21.0% of patients.

Overall, a total of 1172 TEAEs were reported in 451 (55.7%) of patients during the course of this study. The incidence and number of TEAEs was lower with CHF 6532 10 mg (240 events in 50.5% of patients) than with the other treatments (ranging from 286 events in 55.6% of patients to 328 events in 58.9% of patients). Most events were mild or moderate, with 23 severe events. The most common SOCs, reported in > 10% of patients with any treatment, were Respiratory, Thoracic and Mediastinal Disorders (ranging from 24.5% to 33.5% of patients across treatment groups) and Infections and Infestations (ranging from 24.1% to 32.7% of patients across treatment groups). Asthma (PT for reported asthma exacerbations) was reported in 20.5% to 26.6% of patients across treatment groups. The PTs other than asthma (i.e. exacerbation of asthma) reported in > 5% of patients with any treatment were nasopharyngitis (in 7.4% to 9.9% of patients across treatment groups), corona virus infection (in 4.4% to 9.3% of patients across treatment groups) and headache (in 4.0% to 7.3% of patients across treatment groups).

The incidence of serious TEAEs was similar across treatments (ranging from 3.4% to 5.5% of patients). Serious TEAEs were most commonly reported from the SOCs Infections and Infestations (1.7% of patients overall) and Respiratory, Thoracic and Mediastinal Disorders (1.6% of patients overall), with asthma being the most common event by PT (ranging from 1.0% to 2.5% of patients

across treatment groups). Two serious events of severe intensity (PTs: corona virus infection and asthma) in 1 patient with placebo led to death; neither was assessed as related to the study treatment and study treatment was discontinued due to both events. Three other events (PTs: asthma with CHF 6532 10 mg, atrial fibrillation with CHF 6532 25 mg and psychomotor hyperactivity with placebo) led to permanent study treatment discontinuation in 3 patients. None of the serious TEAEs was assessed as related to study treatment. Most events were moderate or severe in intensity and had resolved by the end of the study.

Adverse drug reactions were reported at a similar, low incidence across treatment groups (ranging from 2.4% to 4.4%) and were most commonly reported from the SOC Gastrointestinal Disorders (2.1% of patients overall), with nausea and abdominal pain upper being the most commonly reported PTs (ranging from 0.5% to 1.5%, and 0.5% to 1.0% of patients across treatment groups, respectively). All other ADRs were reported for not more than 1 patient with any treatment. The ADRs reported with CHF 6532 but not with placebo included flatulence, abdominal pain, diarrhoea, rash, headache, alopecia, somnolence, hepatic steatosis, hypersensitivity, eczema, irritable bowel syndrome and decreased appetite. All ADRs were mild or moderate in intensity. Four events led to study treatment discontinuation in 4 patients (PTs: hypersensitivity and hepatic steatosis, both with CHF 6532 25 mg, and abdominal pain upper [2 events] with CHF 6532 50 mg and placebo). Most ADRs had resolved or were resolving at the end of the study, including the events leading to study treatment discontinuation; the PTs ongoing at the end of the study were flatulence, nausea, alopecia, irritable bowel syndrome, cough and dyspnoea.

The proportion of patients who discontinued the study treatment permanently was low and similar across treatment groups, (ranging from 0.5% to 1.5% of patients). Most TEAEs leading to study treatment discontinuation were moderate or severe in intensity and resolved or were resolving by the end of the study.

In the analysis of TEAEs stratified by age group, a total of 26 TEAEs were experienced by 7 (31.8%) adolescents, of which 1 event (PT: bradycardia) in 1 patient was serious and 1 event (PT: irritable bowel syndrome) in 1 patient was assessed as related to study treatment, both with CHF 6532 50 mg. There were no TEAEs leading to study discontinuation or death in adolescents.

Most patients did not show changes of clinical concern in standard haematology, biochemistry, vital signs and 12-lead ECG assessments with the study treatments. Mean changes from baseline and mean changes from pre-dose to 10 mins post-dose in SBP and DBP were minimal and similar across time points with all treatments (ranging from -1.7 to 2.6 mmHg and -0.8 to 1.0 mmHg, respectively for SBP, and -1.0 to 0.7 mmHg and -1.1 to -0.6 mmHg, respectively for DBP).

Mean changes from baseline in ECG parameters were generally minimal and similar across time points with all treatments (ranging from 0.0 to 3.8 beats per minute for HR, -3.1 to 2.2 ms for QTcF, -2.0 to 4.5 ms for PR, -1.4 to 1.9 ms for the QRS and -3.1 to 2.2 ms for the QT interval). Abnormalities in QTcF at any time point after baseline were reported in 1 male at Week 4 pre-dose and 1 female at the ETD visit.

Most patients presented normal or non-clinically significant values at most time points for haematology and biochemistry parameters. Most shifts from normal values at baseline to high or low values at Week 26 and/or Week 52 were observed in fewer than 10 patients per treatment group for each parameter.

Conclusion:

In this phase III randomised controlled study, CHF 6532 did not show an effective reduction in the rate of moderate and severe exacerbations compared to placebo in patients with uncontrolled severe eosinophilic asthma. The effect of CHF 6532 doses on lung function parameters, QoL and asthma control was similar to that of placebo. The treatments were well tolerated and there were no safety issues during the study.

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