2.0 SYNOPSIS

Name of Sponsor/Company: AstraZeneca	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use Only)*
Name of Finished Product: Tudorza-Plus™ (formoterol fumarate)	**Volume:**	
Name of Active Ingredient: S-(+)-1-[3-dimethyl-aminopropyl]-1-(p-fluorophenyl)-5-phthalancarbonitrile oxalate	**Page:**	

Study Number: LAC-MD-21	
Title of Study: Phase II, Randomized, Placebo-Controlled, Double-blind, Double-Dummy, 5 Period Complete Cross-over Study of the Bronchodilator Effects of Formoterol Fumarate Inhalation Powder in Patients with Mild to Moderate Asthma	
Investigators:	
Study Centers:	
Publication (reference): Not applicable.	
Study Period (years): First Patient First Visit: 26 Jun 2012 Last Patient Last Visit: 09 Feb 2013	**Development Phase:** 2
Objective: To compare the bronchodilator effect of formoterol fumarate using the Pressair dry-powder inhaler and the Foradil Aerolizer using serial spirometry	
Study Design: A multicenter, randomized, double-blind, double-dummy, placebo-controlled, 5-period complete crossover pharmacodynamic study. Patients were randomized and received treatments twice daily for 2 weeks. A 9 to 13 days (+ or - 2 days) washout period was required between all periods.	
Diagnosis and Main Criteria for Inclusion: Male and female outpatients aged 18 years or older with mild to moderate asthma (forced expiratory volume in 1 second [FEV_1] ≤ 85% and ≥ 60% of predicted) controlled with a stable dose of inhaled corticosteroids who demonstrate reversibility to albuterol during the screening period.	
A total of 408 patients were screened for the study, and 174 (42.6%), were randomized to treatment. All randomized patients were included in the Safety and Intent-to-Treat (ITT) populations. The Screened Population consisted of all patients who completed Visit 1 assessments and were assigned a screening number. The Randomized Population consisted of all patients in the Screened Population who were randomized to a treatment sequence. The Safety Population consisted of all patients in the Randomized Population who took at least 1 dose of double-blind investigational product. The ITT Population consisted of all patients in the Safety Population who had a baseline and at least 1 postbaseline FEV_1 assessment	
Investigational Product, Dose and Mode of Administration, Lot Number: Please note: Throughout this study, the Sponsor's multidose dry-powder inhaler is referred to by its new intended US trademark name, Pressair. This device was previously referred to as the Inhaler at the end of Phase 2 studies, and it is still referred to by the name Genuair in Europe and the rest of the world. Pressair, Genuair, and Inhaler all represent the exact same device. Formoterol fumarate inhalation powder 6 µg orally (formoterol 6 µg) via the Pressair dry-powder inhaler (DPI) twice daily, Lot No. L00006454 Formoterol fumarate inhalation powder 12 µg orally (formoterol 12 µg)by via the Pressair DPI twice daily, Lot No. L00006324	
Reference Therapy, Dose and Mode of Administration, Lot Number: Placebo, administered by inhalation via the Pressair DPI, twice daily, Lot Nos. L00000650 and L000006670 Formoterol fumarate inhalation powder 12 µg orally (Foradil 12 µg) via Foradil Aerolizer, twice daily, Lot No. L000006454 (Pouches) Formoterol fumarate inhalation powder 24 µg orally (Foradil 24 µg) via Foradil Aerolizer, twice daily, Lot No. L000006324 (Pouches) and L000006455 (12 µg capsule)	
Rescue Therapy, Dose and Mode of Administration, Lot Number: ProAir® HFA (Albuterol Sulfate) Inhalation Aerosol, 90 µg orally, Lot No. L000006391	
Duration of Treatment: 2 weeks	

.

Criteria for Evaluation:

Efficacy

Primary: Change from baseline in normalized FEV_1 AUC_{0-6} after the morning dose of investigational product at Day 14

Secondary: Change from baseline in normalized FEV_1 AUC_{0-6} after the morning dose of investigational product at Day 1 across treatment periods and change from baseline in FEV_1 at each specific time point at Days 1 and 14 across treatment periods

Safety

Adverse events recording, physical examinations, clinical laboratory evaluations (hematology, chemistry, urinalysis), electrocardiograms, vital signs

Statistical Methods:

Disposition: All patient disposition analyses were based on the Screened, Randomized, Safety, and ITT Populations.

Demographics and Other Baseline Characteristics: Demographic parameters (e.g., age, race, sex, weight, height, body mass index) and other baseline characteristics (asthma history, smoking history, FEV_1, reversibility) were summarized overall by descriptive statistics for the Safety and ITT populations.

Efficacy: All efficacy analyses were based on the ITT Population and no imputation was performed. The primary efficacy parameter was the change from baseline in normalized FEV_1 area under the curve from time 0 to 6 hours (AUC_{0-6h}) after the morning dose of investigational product at Day 14 across treatment periods. The analysis was performed using means of a mixed model for repeated measures (MMRM) with treatment and period as fixed effects and baseline FEV_1 value as a covariate and with change from baseline in normalized AUC_{0-6h} FEV_1 as the dependent variable. The within-patient correlation was modeled using the unstructured covariance matrix in the mixed model.

Safety: Safety parameters (eg, adverse events (AEs), clinical laboratory parameters, vital sign measurements, and electrocardiograms (ECG)) were summarized for each treatment group with descriptive statistics that were based on the Safety Population.

SUMMARY OF RESULTS:

Disposition: A total of 408 patients were screened for eligibility; and 174 patients were randomized into the study. The percentage of randomized patients who completed the study was 90.2% (157/174).

Demographics and Other Baseline Characteristics: The average patient was approximately 45.4 years of age, the majority of patients were white (86.2%) and non-Hispanic (92.5%). Slightly more than half of the patients were female (52.3%). The average weight was 83.9 kg and the average body mass index was 28.9 kg/m^2. The mean bronchodilator reversibility at screening was 18.9% and ranged from 12% to 54% across the total patient population. The majority of patients had moderate asthma (83.3%). Although all patients were nonsmokers at the time of enrollment, 24.7% of the patients were ex-smokers (mean total pack years for ex-smokers was 3.02).

Efficacy Results:

Assay sensitivity was established by showing a higher FEV_1 AUC_{0-6} in the Foradil 24 µg dose over the Foradil 12 µg dose. Based on analysis using by period baseline, the treatment difference between Foradil 24 µg and Foradil 12 µg was 0.037 L ($p = 0.0095$) at Day 1 and at Day 14 the treatment difference was 0.012 L ($p = 0.4179$). Based on analysis using the baseline of Period 1, the treatment difference between Foradil 24 µg and Foradil 12 µg was 0.048 L ($p = 0.0009$) at Day 1 and at Day 14 the treatment difference was 0.021 L ($p = 0.1288$). These data confirm the separation between the 2 Foradil doses.

Day 1 results:

When analyzed using baseline of Period 1 (considered a more appropriate method) , patients treated with Foradil 12 µg showed statistically significant improvement in FEV_1 AUC_{0-6} over patients treated with formoterol 12 µg and formoterol 6 µg (0.036 L, $p = 0.0137$ and 0.086 L, $p < 0.0001$, respectively).

FEV_1 improvements with formoterol 12 µg were statistically significantly lower than those with Foradil 12 µg at 5 minutes and at 1, 2, 3, 4, and 6 hours, but were not statistically significantly lower ($p = 0.0847$) at 30 minutes postdosing. These advantages were not retained after 14 days of treatment as the data support that formoterol 12 µg in Pressair to sustain its brochodilation effect better than that of Foradil 12 µg.

Day 14 results:

When analyzed using the baseline at each treatment period, formoterol 12 µg and 6 µg produced 0.280 L and 0.273 L improvements in bronchodilation compared with 0.308 L improvements attained with the approved dose of Foradil 12 µg. No statistically significant differences were observed between Foradil 12 µg and formoterol 12 µg (adjusted mean difference 0.028 L; $p = 0.0586$).

When analyzed using baseline of Period 1 also, there was no statistically significant difference between treatment with Foradil 12 µg and formoterol 12 µg (0.021 L, $p = 0.1320$).

An analysis of FEV_1 at each specific timepoint at Day 14 (based on baseline of Period 1 only) suggests comparability of efficacy between Foradil 12 µg and formoterol 12 µg. The least squares mean of change from baseline in FEV_1 on Day 14 of Foradil 12 µg was 0.009 L (p = 0.6505) lower than that of formoterol 12 µg at 60 minutes before dosing (trough FEV_1), but numerically higher than that of formoterol 12 µg at all post-dose timepoints by a maximum of 0.028 L (p = 0.0711) at 3 hours postdosing and a minimum of 0.007 L (p = 0.6340) at 6 hours postdosing. It should be noted that formoterol 6 µg had a higher change from baseline in FEV_1 at 3 hours postdose than formoterol 12 µg by 0.011L. There were no statistically significant treatment differences between formoterol 12 µg and formoterol 6 µg at any of the specific timepoints.

Because formoterol 12 µg in Pressair is to be used for chronic treatment in the FDC, the data at Day 14 are more appropriate for interpretation of the dose effects.

The FEV_1 data support that the advantage of Foradil 12 µg over formoterol 12 µg on Day 1 decreased in magnitude on Day 14 due to the observation that formoterol 12 µg retained its bronchodilation effect over 14 days of treatment better than that of Foradil 12 µg.

Safety Results:

TEAE frequency was highest in the Foradil 24 µg treatment (24.6%). Tremor and feeling jittery were the most frequently reported preferred terms, with higher frequencies in the Foradil 24 µg treatment (6.0% and 3.6%, respectively) compared to the other active treatments (range: 0.6%-1.2% for tremor and 1.2% for feeling jittery). Two patients in the Foradil 12 µg treatment experienced SAEs (ankle fracture in 1 patient and osteoarthritis in the other patient); both SAEs were judged to be "not related" to investigational product by the Investigator. A total of 9 patients discontinued because of TEAEs: 6 (3.6%) of patients during treatment with Foradil 24 µg, and 1 (0.6%) each during each treatment with Foradil 12 µg, formoterol 12 µg, and formoterol 6 µg. No patients discontinued treatment because of AEs during placebo treatment. There were no deaths during the study.

Although the frequency of TEAEs and AEs that led to discontinuations (ADOs) were higher in Foradil 24 µg treatment, the rates of TEAEs and ADOs in Foradil 12 µg, formoterol 12 µg via Pressair, and formoterol 6 µg via Pressair were comparable with placebo.

No clinically meaningful differences in clinical laboratory parameters, vital signs, and ECG from baseline to end of treatment were observed during any of the treatments.

When using the QTcF correction for the QT interval, differences in the frequency of PCS ECG under different treatments were not observed.

CONCLUSIONS:

Date of the Report 24 Feb 2014