2. SYNOPSIS

Name of Sponsor/Company: Teva Global Branded Products R&D, Inc.	**Individual study table referring to part of dossier in which the individual study or study table is presented**	(For National Authority Use Only)
Name of Finished Product: Fluticasone propionate Multidose Dry Powder Inhaler (Fp MDPI)	**Volume:**	
Name of Active Ingredient: Fluticasone propionate	**Reference:**	

Title of Study: A 12-Week Dose-Ranging Study to Evaluate the Efficacy and Safety of Fp SPIROMAX® (Fluticasone Propionate Inhalation Powder) Administered Twice Daily Compared With Placebo in Adolescent and Adult Subjects With Persistent Asthma Uncontrolled on NonSteroidal Therapy.

Investigators and Study Centers: The study was conducted at 188 centers (7 in Bulgaria, 4 in Croatia, 12 in Hungary, 11 in Israel, 7 in Poland, 2 in Serbia, 3 in Spain, 14 in the Ukraine, and 128 in the USA) by 188 investigators. A complete list of investigators and their affiliations is included in the clinical study report.

Publication (reference): Results from this study have not been published at the time of approval of this report.

Study Period: 12 January 2012 to 10 July 2013 Phase of Development: 2

Primary Objective: The primary objective of the study was to evaluate the dose response, efficacy and safety of 4 different doses of fluticasone propionate (12.5, 25, 50, and 100 mcg) delivered as Fp SPIROMAX® Inhalation Powder (hereafter called Fp MDPI) when administered twice daily in subjects 12 years of age and older with persistent asthma who are uncontrolled on nonsteroidal therapy.

Number of Subjects (Planned and Analyzed): For this study, 600 subjects were planned to be enrolled; 622 were randomized into the active treatment period; data from 611 subjects were analyzed for efficacy and data from 622 subjects were analyzed for safety.

Diagnosis and Main Criteria for Inclusion: Subjects were included in the study if all of the following main criteria were met (not all inclusive):

- male or female 12 years and older, as of the screening visit (SV). Male or female 18 years and older, as of the SV, in countries where local regulations or the regulatory status of study drug permitted enrollment of adults only
- asthma diagnosis: asthma as defined by the National Institutes of Health (NIH)
- severity of disease: a best forced expiratory volume in 1 second (FEV_1) of 40% through 85% of the predicted normal value during the SV
- reversibility of disease: demonstrated a ≥15% reversibility of FEV_1 within 30 minutes following 2 to 4 inhalations of albuterol/salbutamol inhalation aerosol (if required, spacers were permitted for reversibility testing only) at the SV

- current asthma therapy: must not include inhaled corticosteroids during the 6 weeks prior to the SV

Main Criteria for Exclusion: Subjects were excluded from participating in this study if 1 or more of the following main criteria were met (not all inclusive):

- history of life-threatening asthma defined for this study as an asthma episode that required intubation and/or was associated with hypercapnea, respiratory arrest, or hypoxic seizures
- culture-documented or suspected bacterial or viral infection of the upper or lower respiratory tract, sinus, or middle ear that was not resolved within 2 weeks of the SV
- any asthma exacerbation requiring oral corticosteroids within 3 months of the SV. A subject must not have had any hospitalization for asthma within 6 months prior to the SV
- clinical visual evidence of oral candidiasis at the SV
- use of systemic, oral or depot corticosteroids within 12 weeks prior to the SV
- use of immunosuppressive medications within 4 weeks prior to the SV and during the study
- use of potent cytochrome P450 isoenzyme 3A4 (CYP3A4) inhibitors (eg, ritonavir, ketoconazole, itraconazole) within 4 weeks prior to the SV. Mild and moderate CYP3A4 inhibitors were permitted

Main Criteria for Randomization: At the randomization visit, subjects had to continue to meet all of the inclusion criteria and none of the exclusion criteria, as well as the following:

- severity of disease: a best FEV_1 of 40% to 85% of the predicted normal value during the SV
- any combination of asthma symptom scores or albuterol/salbutamol use on at least 4 of the last 7 consecutive days of the run-in period
- no changes in asthma medication (excluding albuterol/salbutamol inhalation aerosol) provided at the SV
- no asthma exacerbation during the run-in period
- compliance with completion of the daily diary

Study Drug Dose, Mode of Administration, Administration Rate, and Batch Number:

Investigational Product: Fluticasone propionate multi-dose dry powder inhaler (Fp MDPI), 12.5, 25, 50, and 100 mcg, 1 inhalation twice daily (total daily doses of 25, 50, 100, and 200 mcg). Batch numbers RD1117 (12.5 mcg), RD1119 (25 mcg), RD1113 (50 mcg), and RD1115 (100 mcg)

Reference Therapy Dose, Mode of Administration, and Administration Rate:

Placebo: placebo MDPI, 1 inhalation twice daily. Batch number RD1105 (placebo)

Active comparator: FLOVENT® DISKUS® 100 mcg, 1 inhalation twice daily (total daily dose 200 mcg)

Rescue Therapy Dose, Mode of Administration, and Administration Rate:

Rescue mediation: albuterol/salbutamol hydrofluoroalkane (HFA) multidose inhaler (MDI) (90 mcg/actuation) for use on an as needed basis for the relief of asthma symptoms

Method of Blinding: Subjects were randomly assigned to 1 of the 6 treatment groups (Fp MDPI 12.5, 25, 50, or 100 mcg, placebo MDPI, or FLOVENT DISKUS) in a 1:1:1:1:1:1 ratio using a stratified permuted block randomization procedure with pharmacokinetic cohort participation as the stratification variable. The randomized treatment and medication kit number were assigned through an interactive voice response system (IVRS)/interactive web response system (IWRS). Fp MDPI and placebo MDPI were administered in a double-blind fashion, and FLOVENT DISKUS was administered in an open-label fashion.

Duration of Treatment:

Run-in period: 14 days ±2 days (2 weeks), during which subjects continued using their current asthma medications and also administered 1 inhalation of placebo MDPI (single-blind) twice daily.

Treatment period: 84 days ±2 days (12 weeks) during which subjects received the double-blind or open-label treatment to which they were randomized.

Overall: 98 days ±4 days (approximately 15 weeks)

General Design and Methodology: This was a randomized, double-blind, placebo- and open-label active-controlled, parallel-group, multicenter, dose-ranging study in male and female subjects aged 12 years and older with asthma who were uncontrolled on nonsteroidal therapy.

Primary Efficacy Measure(s) and Endpoint(s): The primary efficacy measure was trough FEV_1 measured electronically by spirometry at morning investigational site visits, before administration of the morning dose of study drug and before albuterol/salbutamol administration. The primary efficacy endpoint was the change from baseline in trough (morning [AM] predose and pre-rescue bronchodilator) FEV_1 over the 12-week treatment period.

Secondary Efficacy Measures and Endpoints: The secondary efficacy endpoints were as follows:

Secondary and other efficacy measures included peak expiratory flow (PEF), rescue medication use, asthma symptoms, the asthma control test (ACT), and asthma exacerbations.

Secondary efficacy endpoints were:

- change from baseline in weekly average of daily trough (predose and pre-rescue bronchodilator) AM PEF over the 12-week treatment period
- change from baseline in weekly average of daily evening (PM) PEF over the 12-week treatment period
- change from baseline in the percentage of rescue-free 24-hour periods during the 12-week treatment period

- time to withdrawal due to meeting stopping criteria for worsening asthma during the 12-week treatment period

Safety Variables: Safety was assessed by evaluating reported adverse events (including deaths, serious adverse events, and withdrawals due to adverse events), results of clinical laboratory tests (serum chemistry, hematology, and urinalysis), vital signs (blood pressure and pulse) values, electrocardiogram (ECG) results, physical and oropharyngeal examination findings, and concomitant medication usage.

Pharmacokinetics: Pharmacokinetic endpoints for fluticasone propionate were assessed predose and up to 12 hours postdose at the first treatment visit in approximately 20% of subjects (the pharmacokinetic cohort) The parameters assessed were area under the plasma concentration-time curve from time zero to the time of the last measurable concentration (AUC_{0-t}), maximum observed plasma concentration (C_{max}), and time of maximum observed concentration (t_{max}).

Statistical Considerations: Populations analyzed were:

Intent-to-Treat (ITT) Population: included all randomized subjects; treatment was assigned based on the treatment to which subjects were randomized.

Full Analysis Set (FAS): included all subjects in the ITT population who received at least 1 dose of study drug and had at least 1 postbaseline trough (AM predose and pre-rescue bronchodilator) FEV_1 assessment. In this analysis set, treatment was assigned based upon the treatment to which subjects were randomized.

Per-Protocol (PP) Population: included all data from randomized subjects prior to experiencing a major protocol violation.

Pharmacokinetic Analysis Set: a subset of the PP population, including subjects selected for pharmacokinetic assessments

Safety Population: included all randomized subjects who received at least 1 dose of study drug (treatment was assigned based upon the treatment subjects actually received)

The FAS was the primary analysis set for efficacy analyses and the ITT population was the supportive population. The primary efficacy analysis was also performed on the PP set.

The primary analysis of the change from baseline in trough (AM predose and pre-rescue bronchodilator) FEV_1 over the 12-week treatment period was performed using a mixed model repeated measures (MMRM) analysis with effects due to baseline trough FEV_1, sex, age, visit, treatment, and visit-by-treatment interaction. A fixed-sequence testing procedure was employed to control the overall Type I error rate at the 0.05 level. Specifically, the 2-sided linear in log-dose time-averaged trend test was first performed at the 0.05 level of significance. Only if this trend test demonstrated overall efficacy of Fp MDPI (a significantly positive trend), was the highest Fp MDPI dose (100 mcg twice daily) to be compared with placebo with a 2-sided test at the 0.05 level of significance. If the highest Fp MDPI dose was found to be effective (resulting in a significantly greater time averaged FEV_1 mean than placebo), the next highest Fp MDPI dose (50 mcg twice daily) was compared with placebo with a 2-sided test at the 0.05 level of significance. The testing was to proceed through the lower Fp MDPI doses until an Fp MDPI dose was not found to be effective or all the Fp MDPI doses had been tested. The study was to be considered positive if the trend test was positive and the test involving the highest Fp MDPI dose (100 mcg twice daily) indicated this dose results in a

significantly greater time averaged FEV_1 mean than placebo, regardless of the results of the tests for the other Fp MDPI doses compared with placebo.

Supportive analyses included comparison of Fp MDPI with placebo after 12 weeks of therapy based on MMRM, comparison of Fp MDPI with placebo after 12 weeks of therapy based on analysis of covariance (ANCOVA), and comparison of Fp MDPI and placebo with FLOVENT DISKUS (MMRM and ANCOVA).

The change from baseline in weekly average of daily trough AM PEF and PM PEF, over the 12-week treatment period, was analyzed via MMRM and an exploratory linear in log-dose trend test of overall efficacy of Fp MDPI doses was also done. The change from baseline in the percentage of rescue-free 24-hour periods was analyzed with a marginal (also called population averaged) logistic model, with the response being the proportion of rescue free 24 hour periods. A conditional logistic model (also called a subject specific or mixed model) was also fit to the data. The time to withdrawal due to stopping criteria was compared between the treatment groups with the log rank test. The Kaplan-Meier estimate of the probability of remaining in the study at week 12 with 95% confidence interval (CI) was presented by treatment group.

Summary of Results

Subject Disposition and Demography: A total of 1903 subjects with asthma were screened, of whom 909 received run-in placebo medication. A total of 622 subjects with asthma were randomly assigned to treatment (103 subjects each in the Fp MDPI 12.5 and 100 mcg groups and 104 subjects each in the Fp MDPI 25 and 50 mcg groups, the placebo group and the FLOVENT DISKUS group). Of these, all 622 subjects received at least 1 dose of study drug and were evaluable for safety; 611 (98%) subjects were evaluable for efficacy; and 483 (78%) subjects completed the study.

The average age of the subjects was 39.9 years (range 12 to 81 years). The majority (85%) of subjects were white. There were slightly fewer males (42%) than females (58%).

Efficacy Results: Baseline characteristics for efficacy variables were generally similar across treatment groups.

FEV_1: The primary efficacy endpoint was the change from baseline in trough (AM predose and pre-rescue bronchodilator) FEV_1 over the 12-week treatment period. The primary efficacy analysis was carried out on the FAS.

In all treatment groups there was an increase (improvement) in least squares (LS) mean FEV_1 from baseline over the 12-week treatment period, with a significantly greater change seen with Fp MDPI 25, 50, and 100 mcg (LS mean change 0.229 L, 0.243 L, 0.267 L, respectively) compared with placebo (LS mean 0.118 L, $p \leq 0.0086$). The change from baseline in trough FEV_1 over the 12-week treatment period with Fp MDPI 12.5 mcg (0.170 L) was not statistically significantly different from placebo.

Supportive analyses on the ITT and PP populations, and on the change in FEV_1 from Baseline to Week 12 (MMRM and ANCOVA) were all statistically significant in favor of Fp MDPI for the 3 highest doses of Fp MDPI compared with placebo, but not for the lowest dose of 12.5 mcg. Compared with placebo, the increase in FEV_1 from baseline to weeks 1, 2, 4, 8, and 12 was statistically significantly greater with Fp MDPI 50 and 100 mcg at each timepoint from week 1 onwards, and with Fp MDPI 25 mcg at weeks 1 and 4.

With FLOVENT DISKUS, the LS mean increase in FEV_1 from baseline over the 12-week treatment period was intermediate between the Fp MDPI doses of 25 and 50 mcg, and there was no statistically significant difference

between the 25, 50, and 100 mcg Fp MDPI dose groups and FLOVENT DISKUS in any analyses of the change in FEV_1.

Peak Expiratory Flow: There was an improvement (increase) from baseline in all PEF endpoints assessed, which was greater with all active treatments than with placebo (weekly average of daily trough AM PEF and PM PEF over the 12-week treatment period, daily trough AM PEF over the first 14 days on study drug, daily trough AM PEF at all weeks (1 through 12), weekly average of daily trough AM PEF over weeks 1 through 4, 5 through 8 and 9 through 12, and weekly average of daily trough AM PEF at endpoint). Compared with placebo, the changes were statistically significantly greater with Fp MDPI 12.5 mcg for all analyses, for Fp MDPI 50 mcg for all analyses except the change in daily trough AM PEF over weeks 9 through 12, and with FP MDPI 100 mcg for the increase in AM PEF over the 12-week treatment period, over the first 14 days of treatment, and over weeks 1 through 4 and 5 through 8. For Fp MDPI 25 mcg the only statistically significant difference compared with placebo were in daily trough AM PEF over the first 14 days on study drug and the change from baseline in daily trough AM PEF at weeks 1 and 5.

There was no statistically significant difference between FLOVENT DISKUS and any Fp MDPI dose group in any of the analyses concerning AM and PM PEF.

Asthma Control Test: The LS mean ACT score improved (increased) from baseline at all timepoints (weeks 4, 8, and 12) and over the whole treatment period (weeks 1 through 12) in all treatment groups. The increases were statistically significantly greater with all active treatments at all timepoints compared with placebo. The increase in ACT with FLOVENT DISKUS was statistically significantly greater than that with Fp MDPI 25 mcg and 50 mcg over the whole treatment period, and than Fp MDPI 50 mcg at week 8 and week 12.

Time to Withdrawal Due to Meeting Stopping Criteria for Worsening Asthma: In all groups, the most common stopping criteria which led to withdrawal was that during any 7-day treatment window, the subject had experienced more than 3 days in which the PEF had fallen below the PEF stability limit calculated at treatment visit 1 (TV1). Compared with placebo, there was a statistically significantly higher probability of remaining in the study at week 12 with any dose of Fp MDPI ($p \leq 0.0053$) and with FLOVENT DISKUS ($p=0.0001$). There was no significant difference between Fp MDPI (any dose) and FLOVENT DISKUS.

Rescue Medication Use: There was an improvement in rescue medication use in all groups from baseline which was statistically significantly greater with all Fp MDPI doses than placebo for the change from baseline in the percentage of rescue-free 24-hour periods over the 12-week treatment period (conditional model analysis), total daily (24-hour) number of inhalations of albuterol/salbutamol over the first 14 days on study drug, weekly average of total daily (24-hour) use of albuterol/salbutamol inhalation (number of inhalations) over weeks 1 through 12 and to endpoint. A marginal logistic model found an increase in the percentage of rescue-free 24-hour periods in all groups from baseline over the 12-week treatment period which was greater in the Fp MDPI groups than the placebo group, but this difference was only statistically significant with Fp MDPI 12.5 mcg versus placebo ($p=0.03825$).

There was no statistically significant difference between FLOVENT DISKUS and any Fp MDPI dose group in any of the analyses concerning rescue medication use.

Asthma Symptoms: There was an increase in the percentage of symptom-free 24-hour periods in all groups from baseline over the 12-week treatment period which was greater with all doses of Fp MDPI compared with placebo. This difference was only statistically significant with Fp MDPI 12.5 mcg versus placebo in the marginal model analysis, but was statistically significant for all Fp MDPI doses versus placebo using a conditional model analysis.

Safety Results:

Adverse Events: Adverse event rates did not appear to be dose-related across the active treatment groups. During the double-blind treatment period, approximately one third of subjects in each of the 6 treatment groups experienced adverse events. There were ≤6 (6.0%) subjects in any treatment group who had adverse events related to treatment and these mostly occurred in the respiratory, thoracic, and mediastinal disorders system organ class (SOC). Most treatement-related adverse events were mild and only 1 adverse event, asthma, was severe and considered related to treatment (placebo).

Eight serious adverse events were reported by 7 subjects (1.1%) during the treatment period: 2 subjects each with Fp MDPI 100 mcg, placebo, and FLOVENT DISKUS and 1 subject with Fp MDPI 50 mcg. Only 1 serious adverse event, exacerbation of asthma in a placebo subject, was considered to be related to treatment and this subject discontinued the study due to this event.

The discontinuation rate due to adverse events was low: 1 subject (<1%) in the Fp MDPI 100 mcg group discontinued due to adverse events of anemia and uterine hemorrhage, 2 subjects (2%) in the FLOVENT DISKUS group discontinued due to adverse events of respiratory tract infection and upper respiratory tract infection (URI), and 2 subjects (2%) in the placebo group discontinued due to adverse events of asthma and hypertension.

No deaths occurred during the study.

Clinical Laboratory Findings: The majority of subjects in each treatment group had normal clinical laboratory findings at baseline. There were no clinically meaningful trends in mean changes from baseline for any parameters in serum chemistry, hematology, or urinalysis in any of the treatment groups. Shifts in clinical laboratory values from the normal range at baseline to outside the normal range occurred with similar low frequency across the treatment groups. No clinical laboratory value was identified by the investigator as a clinically significant abnormality and there were no serious adverse events or discontinuations due to potentially clinically significant changes.

Vital Signs: No safety signals associated with vital signs or ECGs were observed.

Oropharyngeal Examination: Only 1 subject in the Fp MDPI 25 mcg group had a positive examination for oral candidiasis and a positive swab test result.

Asthma exacerbations: Asthma exacerbations were reported for more subjects in the placebo group (8 subjects, 8.0%) compared to the active treatment groups (≤5 subjects per group). The only severe asthma exacerbation occurred in 1 subject in the placebo group. All other exacerbations of asthma were of mild or moderate intensity.

Pharmacokinetics Results: In the analysis of pharmacokinetics, fluticasone propionate AUC0-t and Cmax increased with increasing dose of Fp MDPI and comparisons of $AUC_{0\text{-}t}$ and C_{max} between doses of Fp MDPI indicated approximately dose proportional increases in both parameters across the doses levels tested (Fp MDPI 12.5, 25, 50, and 100 mcg). On a dose-normalized basis, the systemic exposures from the Teva MDPI were consistently higher than expected based on the systemic exposure from 100 µg delivered via the DISKUS. The t_{max} was similar across treatments.

Conclusions: The efficacy of Fp MDPI was demonstrated, with statistically significant improvements with at least 1 dose of Fp MDPI versus placebo in all efficacy variables assessed (FEV_1, PEF, ACT, rescue medication use, asthma symptoms, and time to withdrawal due to meeting stopping criteria). Effects were seen as early as the first week and maintained over 12 weeks. A dose response was suggested in some variables, most notably FEV_1, and efficacy was generally comparable between Fp MDPI (all doses) and FLOVENT DISKUS, but with lower systemic exposure with Fp MDPI 12.5, 25, and 50 mcg compared to FLOVENT DISKUS. The safety profiles of Fp MDPI 12.5, 25, 50, and 100 mcg were comparable to the established profile of FLOVENT DISKUS with no new safety signals observed.