1. 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: Tiotropium HFA BAI SPIRIVA® HandiHaler® Respimat® Soft Mist™ Inhaler	**Volume:**	
Name of Active Ingredient: Tiotropium bromide	**Reference:**	

Title of Study: A Randomized, Open-Label, Repeat Dosing (7 days), Four-Period Crossover Study to Compare the Pharmacokinetics, Efficacy and Safety of Tiotropium Bromide Delivered via Breath Actuated Inhaler (BAI), SPIRIVA® HandiHaler® and Respimat® Soft Mist™ Inhaler (SMI) in Subjects with Chronic Obstructive Pulmonary Disease (COPD)

Investigators and Study Centers: The study was conducted at 5 centers in Germany by 5 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: 03 January 2013 to 03 July 2013 **Phase of Development:** 2a

Primary Objective: The primary objective of the study was to assess and compare the pharmacokinetics of tiotropium delivered via BAI (4.5 mcg or 9.0 mcg), SPIRIVA HandiHaler (18 mcg) and Respimat SMI (5.0 mcg) following repeat dosing for 7 days in subjects with COPD.

Secondary Objectives: The secondary objectives of the study were the following:

- To evaluate the efficacy of tiotropium hydrofluoroalkane (HFA) inhalation aerosol delivered via BAI (4.5 mcg or 9.0 mcg) compared with tiotropium bromide delivered via SPIRIVA HandiHaler (18 mcg tiotropium) and Respimat SMI (5.0 mcg tiotropium) in subjects with COPD following repeat dosing for 7 days.
- To evaluate the safety and tolerability of tiotropium HFA BAI.

Number of Patients (Planned and Analyzed): For this study, 36 patients were planned to be enrolled; data from 35 patients were analyzed for efficacy and data from 36 patients were analyzed for safety.

Diagnosis and Main Criteria for Inclusion: Patients were included in the study if all of the inclusion criteria were met. The main inclusion criteria included:

- Written informed consent signed and dated by the subject before conducting any study related procedure.
- Male or female subjects 40–80 years of age, as of the Screening Visit (SV)
- Diagnosis of COPD as defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) Guidelines.
- A pre-bronchodilator peak inspiratory flow (PIF) rate ≥30 L/min as measured with the In-Check™ DIAL training device.

- A measured post-bronchodilator (ipratropium bromide) forced expiratory volume in one second (FEV_1) >30% and <80% of predicted normal for height, age and gender at the SV. National Health and Nutrition Examination Survey (NHANES) III predicted values were used.
- A measured post-bronchodilator (ipratropium bromide) FEV_1/forced vital capacity (FVC) <0.70 at the SV

Main Criteria for Exclusion: Patients were excluded from participating in this study if 1 or more of the exclusion criteria were met. The main exclusion criteria included:

- Pregnancy, nursing, or plans to become pregnant or donate gametes (ova or sperm) for in vitro fertilization during the study period or for 30 days following the subject's last study related visit (for eligible subjects only, if applicable).
- History or current evidence (as determined by medical history, physical examination, clinical laboratory assessments and electrocardiogram [ECG]) of a clinically significant or uncontrolled disease including, but not limited to: cardiovascular (eg, uncontrolled hypertension, congestive heart failure, known aortic aneurysm, clinically significant cardiac arrhythmia or coronary heart disease), hepatic, renal, haematological, neuropsychological, endocrine (eg, uncontrolled diabetes mellitus, uncontrolled thyroid disorder, Addison's disease, Cushing's syndrome), gastrointestinal (eg, poorly controlled peptic ulcer, gastroesophageal reflux disease) or pulmonary (other than COPD such as asthma, sarcoidosis, non-cystic fibrosis bronchiectasis, cystic fibrosis, bronchopulmonary dysplasia or a diagnosis of alpha 1-antitrypsin deficiency). Significant was defined as any disease that, in the opinion of the investigator, would put the safety of the subject at risk through participation, or which could affect the endpoint analysis if the disease/condition exacerbated during the study.
- History of a life-threatening COPD exacerbation – defined for this study as a COPD episode that required intubation and/or was associated with hypercapnia, respiratory arrest or hypoxic seizures.
- Thoracotomy with pulmonary resection.
- Occurrence of a COPD exacerbation, which was not resolved by 14 days prior to randomization.

Randomization Criteria: Patients had to meet the following randomization criteria before being randomized:

- Subject continued to be in general good health, meeting the selection criteria.
- Subject had not experienced an adverse event that would result in failure to continue to meet selection criteria.
- Subject had not used any of the prohibited concomitant medications during the previous period.
- Subject had not suffered from an exacerbation of COPD or an upper or lower respiratory infection within the 14 days prior to randomization.

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

Investigational Product:

- Treatment A (tiotropium HFA BAI – 4.5 mcg): Tiotropium bromide HFA inhalation aerosol via BAI (administered as 1 inhalation [4.5 mcg/inhalation] once daily in the morning for 7 days – total daily dose of 4.5 mcg/day). The batch number was 318M-12-008.

- Treatment B (tiotropium HFA BAI – 9.0 mcg): Tiotropium bromide HFA inhalation aerosol via BAI (administered as 2 inhalations [4.5 mcg/inhalation] once daily in the morning for 7 days – total daily dose of 9 mcg/day). The batch number was 318M-12-008.

Comparison Drugs:

- Treatment C (SPIRIVA HandiHaler): Tiotropium Bromide Inhalation Powder via HandiHaler (administered as 2 inhalations from 1 capsule [18 mcg tiotropium/capsule] once daily in the morning for 7 days – total daily dose of 18 mcg tiotropium/day). The batch number was 204819.
- Treatment D (SPIRIVA Respimat): Tiotropium Bromide Inhalation Solution via Respimat SMI (administered as 2 inhalations [2.5 mcg tiotropium/inhalation] once daily in the morning for 7 days – total daily dose of 5 mcg tiotropium/day). The batch number was 205097.

Reference Therapy Dose, Mode of Administration, and Administration Rate: Not applicable

Method of Blinding: This was an open label study with no blinding. Enrolled subjects were randomized to 1 of 4 different treatment sequences (ABCD, BDAC, CADB, DCBA) in 1:1:1:1 ratio in accordance with the randomization schedule generated in advance of the study start. Randomization was stratified by study site.

Duration of Treatment: Repeated dosing in 4 Treatment Periods consisting of 7 treatment days each, with a washout period of at least 21 days between Treatment Periods.

General Design and Methodology: This was a multi-center, open-label, randomized, repeat dosing (7 days), 4-period pharmacokinetic/pharmacodynamic crossover study in 36 male or female subjects 40–80 years of age with COPD.

The study consisted of a SV (3 to 14 days prior to randomization); 4 multiple-dose (7-day) Treatment Periods, each consisting of a 2 night/3 day inpatient stay (day 6 to day 8); and a Final Visit (FV). A washout period of at least 21 days occurred between Treatment Periods. The Final / Early Termination Visit (FV/ET) occurred 6–8 days following the last Treatment Period (TP4) or upon early discharge from the study (early termination, ET).

Subjects meeting all entry inclusion criteria and randomization criteria and none of the exclusion criteria were randomized to 1 of 4 treatment sequences (ABCD, BDAC, CADB, DCBA).

Plasma samples for pharmacokinetic analysis were obtained pre- treatment on day 1, and both pre-dose and serially post-dose on day 7. Urine samples were obtained pre-treatment on day 1, and both pre-dose and over 24 hours post-dose on day 7.

At SV, the PIF was measured first and then lung function testing was performed prior to and within 30 minutes after a dose of ipratropium bromide (80 mcg). Spirometry was performed prior to dosing, and following dosing serially over 1 hour on day 1 and over 24 hours on day 7.

Safety was monitored by clinical laboratory examinations, 12-lead ECGs, spirometry (to assess paradoxical bronchoconstriction), physical examination, vital sign measurements, and adverse events.

Primary Pharmacokinetic Measures and Endpoints: The primary pharmacokinetic variables were the area under the plasma concentration-time curve on day 7 from time 0 to 24 hours (AUC_{0-24}) and the maximum observed plasma concentration (C_{max}) for tiotropium.

Secondary Pharmacokinetic Measures and Endpoints: The secondary pharmacokinetic variables and endpoints were as follows:

- AUC_{0-t}

- t_{max}

Other Pharmacokinetic Measures and Endpoints: The other pharmacokinetic variables and endpoints were as follows:

- The cumulative amount of urinary excretion of tiotropium over 24 hours postdose on day 7
- The plasma and urine levels of tiotropium on day 1, at the start of each dosing period/end of each washout

Efficacy Measures and Endpoints: The efficacy variables and endpoints were as follows:

- Trough FEV_1, defined as the average of the values at 23–24 hours post-day 7 dose
- Trough FVC, defined as the average of the values at 23–24 hours post-day 7 dose
- Time to onset of measured effect (>10% improvement in FEV_1 from predose baseline on day 7)
- Time to peak FEV_1
- Forced expiratory volume in one second (FEV_1) area under the curve for the time period 0 to 24 hours postdose (FEV_1 AUC_{0-24})
- FVC AUC_{0-24}
- Peak FEV_1
- Peak FVC
- Rescue medication use within 24 hours prior to study visit assessments and throughout the assessment period on days 1 and 7 of each Treatment Period

Safety Variables: Safety was assessed by the evaluating the following: serial FEV_1 measures (to assess paradoxical bronchoconstriction), rescue medication use (during 60 minutes post-dose on day 1 to use in assessing paradoxical bronchoconstriction), reported adverse events, clinical laboratory test results, vital signs measurements, ECG findings, and physical examination findings.

Statistical Considerations: The pairwise between-group comparisons of AUC_{0-24} and C_{max} was performed using an analysis of variance (ANOVA) model. The ANOVA model was based on the log transformed data and contained fixed effects for sequence, period, and treatment, and a random effect for subject within sequence. The ratio of geometric means for AUC_{0-24} and C_{max}, and the corresponding 90% confidence intervals was provided. Any 2 tiotropium bromide products were considered similar in AUC_{0-24} and C_{max} if the 90% confidence intervals for the geometric mean ratios of AUC_{0-24} and C_{max} were both contained within (0.8, 1.25). The same ANOVA model was used for the analysis of AUC_{0-t} and of the cumulative amount of urinary excretion of tiotropium over 24 hours postdose on day 7. Comparison of t_{max} between treatment groups was based on the Wilcoxon signed rank test applied to the period differences.

The change from baseline in the following efficacy endpoints was analyzed using an analysis of covariance (ANCOVA) model with fixed effects for sequence, period, treatment and gender, a random effect for subject within sequence, and covariates of baseline value and age:

- Trough FEV_1
- Trough FVC
- FEV_1 $AUC_{(0-24h)}$

- FVC $AUC_{(0-24h)}$
- Peak FEV_1
- Peak FVC

A similar nonparametric approach as described for the t_{max} analysis was used to analyze the following 2 efficacy endpoints:

- Time to onset of measured effect (>10% improvement in FEV_1 from predose baseline on day 7)
- Time to peak FEV_1

Summary of Results

Patient Disposition and Demography: A total of 55 subjects with COPD were screened for enrollment into this study. Of the 55 subjects screened, 36 subjects at 5 centers in Germany were enrolled into the study. Of the 19 subjects who were not enrolled, 16 were excluded on the basis of inclusion/exclusion criteria, 1 subject withdrew consent, and 2 subjects were not included due to other reasons. Of the 36 subjects enrolled, 36 subjects received at least 1 dose of study medication and were evaluated for safety in the study; none of the subjects withdrew before taking any study drug.

A total of 2 (6%) subjects withdrew from the study: One subject died during the study, and one subject was discontinued due to a protocol violation.

Pharmacokinetic Results: Both test treatments (tiotropium HFA BAI 4.5 mcg/day and 9 mcg/day) differed from the reference treatments (SPIRIVA HandiHaler 18 mcg/day and SPIRIVA Respimat 5 mcg/day) in the primary pharmacokinetic parameters AUC_{0-24} and C_{max} on day 7 following 7 days of repeated dosing. For the primary parameters, geometric mean ratios were below 1 and the 90% confidence intervals were not within 0.8-1.25, indicating that systemic exposure to tiotropium was less for the test treatments as compared to the reference treatment, and similarity between the test and reference treatments was not demonstrated.

In all comparisons of the pharmacokinetic assessments AUC_{0-24}, C_{max}, AUC_{0-t}, and cumulative urinary excretion of tiotropium in both the primary (pharmacokinetic) and supportive analysis (full analysis set [FAS]) populations, tiotropium exposure was lower in the BAI-treated groups than in the comparators, eg the ratio of the test to reference treatment was less than 1. Additionally, in most cases both the upper and lower limits of the 90% confidence intervals were less than 1. In a few of the comparisons (pharmacokinetics: AUC_{0-24}, AUC_{0-t} and FAS: AUC_{0-24}) of the high dose test treatment (tiotropium HFA BAI 9.0 mcg/day) to SPIRIVA Respimat 5 mcg/day, the confidence interval for the ratio included 1. The comparisons of mean urinary excretion of tiotropium over 24 hours should not be considered as completely quantitative since some urine collections were missed or did not have volumes recorded. All the statistical comparisons for AUC_{0-24}, C_{max}, AUC_{0-t}, and cumulative urinary excretion failed to show similarity between the test and the reference treatments in that none of the confidence intervals fell within the pre-specified limit (0.8-1.25).

The median values for the time to maximum tiotropium concentration in the plasma (t_{max}) following 7 days of repeated dosing was lower for tiotropium HFA BAI 4.5 mcg/day (4.8 minutes) than for all other treatments (5.4 minute). The differences in t_{max} between the test and reference treatments were small (0 to 1.2 minutes), and the 90% confidence intervals limits for the treatment differences were relatively narrow and all included 0. Since t_{max} is a function of both absorption and elimination, and elimination is presumably device-independent, the similarities in t_{max} suggest no differences in absorption.

Pharmacokinetic effects were numerically smaller for the 4.5 mcg than the 9 mcg test treatment and the differences were consistent with the 2-fold difference in the dose. The mean values of AUC_{0-24}, C_{max}, AUC_{0-t}, and cumulative

amount of urinary excretion of tiotropium were approximately 2 to 2.5 times lower for tiotropium HFA BAI 4.5 mcg/day than for tiotropium HFA BAI 9 mcg/day. In all comparisons of the test to reference treatments, the higher dose of the test treatment (tiotropium HFA BAI 9 mcg/day) more closely matched the reference treatments than the lower dose (tiotropium HFA BAI 4.5 mcg/day). In general there was an approximately 2-3-fold difference in the ratios for the higher dose compared to the lower dose. As an example, the AUC_{0-24} ratio for the higher (9 mcg) and lower (4.5 mcg) doses compared to SPIRIVA HandiHaler were 0.666 and 0.246 respectively, and compared to SPIRIVA Respimat were 0.860 and 0.349 respectively.

Pretreatment plasma and urine levels of tiotropium on day 1 (ie, at the start of each dosing period/end of each washout period) were detected at low levels in all treatment groups. These pretreatment levels did not impact the pharmacokinetic analysis, however, in that pharmacokinetic parameters were evaluated on day 7 following a week of dosing which allowed a total of 4 weeks (washout) since the prior Treatment Period. Other analyses were not likely affected since pretreatment levels in both plasma and urine were very low relative to postdose levels.

Overall, lower systemic exposure and lower urinary excretion was observed for tiotropium HFA BAI as compared to the reference treatments. The difference was numerically smaller for 4.5 mcg/day dose than for 9 mcg/day dose, consistent with the 2-fold lower dose administered.

Efficacy Results: Following 7 days dosing, FEV_1 values plotted over 24 hours were generally similar in appearance for all four treatments with the lower dose (4.5 mcg/day) tiotropium HFA BAI appearing quantitatively slightly lower than the other three treatments.

Trough FEV1 and FVC

The principal efficacy endpoints were the trough FEV_1 and the trough FVC values after 7 days of dosing with the trough defined as the average of 2 measurements at 23 h 15 min and 23 h 45 min post-dose. The mean change from baseline trough FEV_1 value after 1 week of dosing (mean period predose–baseline–adjusted trough FEV_1 at 23−24 hours post day 7 dose) showed modest numeric differences with treatment values of 0.10 L (tiotropium HFA BAI 9 mcg/day), 0.07 L (tiotropium HFA BAI 4.5 mcg/day and SPIRIVA HandiHaler 18 mcg/day), and 0.05 L (SPIRIVA Respimat 5 mcg/day). The statistical comparison of the test versus reference differences in trough FEV_1 values resulted in no significant differences with p-values ranging from 0.1182 to 0.9805.

The mean change from baseline trough FVC value after 1 week of dosing (mean period predose baseline adjusted trough FVC at 23-24 hours post day 7 dose) was similar for all treatment groups (all values 0.07-0.08) with no significant differences (p-values ranging from 0.9315 to 0.9828) between test and reference treatments in the statistical comparisons of the differences in trough FVC values.

AUC_{0-24} FEV1 and FVC

The mean values for the FEV_1 $AUC_{0–24h}$ were similar for all treatments ranging from 1.75 Lxh to 2.56 Lxh (1.75 Lxh tiotropium HFA BAI 4.5 mcg/day, 2.2 Lxh SPIRIVA Respimat 5 mcg/day, 2.41 Lxh SPIRIVA HandiHaler 18 mcg/day, and 2.56 Lxh tiotropium HFA BAI 9 mcg/day). Similar to the FEV_1, the FVC $AUC_{0–24h}$ mean values ranged from 1.97 Lxh to 2.95 Lxh (1.97 Lxh tiotropium HFA BAI 4.5 mcg/day, 2.46xh L SPIRIVA HandiHaler 18 mcg/day, 2.54 Lxh tiotropium HFA BAI 9 mcg/day, 2.95 Lxh for SPIRIVA Respimat 5 mcg/day). The statistical comparison of the treatment differences in the mean FEV_1 $AUC_{0–24h}$ and in the mean FVC $AUC_{0–24h}$ showed no significant difference (all p-values >0.3355) between test and reference treatments. Although there were not significant differences, the numeric values for tiotropium HFA BAI 4.5 mcg/day treatment were consistently lower than the other 3 treatments. The results of comparisons for AUCs (FEV_1, FVC) over the first 12 hours postdose ($AUC_{0–12}$) were similar to the comparisons for 24 hours ($AUC_{0–24h}$).

Time to onset of measured effect and time to peak FEV_1

The mean time to onset of measured effect (>10% improvement in FEV_1) on day 7 occurred soonest following treatment with tiotropium HFA BAI 9 mcg/day (0.74 h), with increasing times for SPIRIVA Respimat 5 mcg/day (1.17 h), SPIRIVA HandiHaler 18 mcg/day (1.71 h), and tiotropium HFA BAI 4.5 mcg/day (2.62 h). Differences between treatments were close to zero, and the 90% confidence interval for the differences between the test and reference treatments in the time to onset of measured effect included zero for all comparisons.

The mean times to peak FEV_1 on day 7 were similar for tiotropium HFA BAI 9 mcg/day (5.62 h), SPIRIVA HandiHaler 18 mcg/day (5.23 h), and SPIRIVA Respimat 5 mcg/day (5.10 h), while the time was somewhat longer for tiotropium HFA BAI 4.5 mcg/day (7.62 h). The treatment differences were small, and the 90% confidence interval for the differences between the test and reference treatments in the time to peak FEV_1 included zero for all comparisons.

None of the differences in efficacy variables were statistically significant, when comparing the test and the reference treatments. The rescue medication use was similar for all treatments. Between-subject variability was high.

Overall, these results indicate that the efficacy of both test treatments is comparable to that of the reference treatments. However, this study was not powered to assess efficacy and thus, the collected data should be used as preliminary information.

Safety Results: Presented safety data indicate that treatment with tiotropium HFA BAI at dosages of 4.5 mcg and 9 mcg given once daily was generally safe and well tolerated for at least 7 days in subjects with COPD. There was 1 death during the study, which was due to natural causes and considered to be not related to study medication. No treatment-related other serious adverse events occurred during the study and no subjects withdrew from the study due to adverse events. The most frequently reported adverse event in the study was headache. The study schedule of frequent blood sampling and spirometry assessments may have contributed to the incidence of headaches. Treatment-related headaches were reported for only 3 subjects (per investigator, revised to 1 subject after study closure) and all received the low dose of tiotropium HFA BAI suggesting that it was not drug-related. Other frequently occurring adverse event was asymptomatic decreased FEV_1. Most adverse events were of mild or moderate severity. No marked difference between the test and the reference treatments was observed for the frequency and severity of adverse events. For tiotropium HFA BAI at dosage of 4.5 mcg/day, the incidence of treatment-related adverse events was higher than for the other treatments (18% vs. 6–9%). The difference is attributed to treatment-related headache that was observed in 3 (9%) subjects treated with tiotropium HFA BAI 4.5 mcg/day but was not observed for all other treatments. One subject (3%) treated with tiotropium HFA BAI 4.5 mcg/day reported a single event (Category 4 – Asymptomatic drop in FEV_1) that was possibly related to paradoxical bronchoconstriction. Low frequencies of Category 4 events (0.2–4.3%) have been previously reported for SPIRIVA Respimat in COPD patients. There were no reports of paradoxical bronchoconstriction in any of the treatment groups. No treatment related adverse events associated with clinical laboratory parameters, vital signs, ECG, and physical examination occurred. Use of rescue medication was similar for all treatments.

Conclusions: The systemic exposure to and the urinary excretion of tiotropium on day 7 following 7 days of repeated dosing/administration was less for the test treatments (tiotropium HFA BAI delivered doses 4.5 mcg and 9.0 mcg) than for the reference treatments (SPIRIVA HandiHaler 18 mcg, delivered dose approximately 10.4 mcg and SPIRIVA Respimat delivered dose 5 mcg) and similarity between the test and reference treatments was not demonstrated. Although not directly compared, exposure to 2 doses of tiotropium HFA BAI was generally proportional to the 2-fold difference in dose. There was no effect of delivery device on the absorption rate.

Preliminary information indicated that there was little difference in efficacy between the test and the reference treatments, with the most of the efficacy parameters being similar for the test and the reference treatments. Although

the lower dose of tiotropium HFA BAI tended to be numerically smaller than the other 3 treatments, there were no statistically significant differences in efficacy observed between the test and reference treatments.

Treatment with tiotropium HFA BAI at dosages of 4.5 mcg and 9 mcg given once daily was generally safe and well tolerated for at least 7 days in subjects with COPD. No marked difference between the test and the reference treatments was observed for the frequency and severity of adverse events. No treatment-related adverse events associated with clinical laboratory parameters, vital signs, electrocardiography, and physical examination. Use of rescue medication was similar for all treatments.