2.0 SYNOPSIS

<table>
<tr><td>Name of Company:
AstraZeneca</td><td colspan="2">Individual Study Table Referring to Part of the Dossier: NA</td><td>(For National Authority Use Only)</td></tr>
<tr><td>Name of Finished Product:
Aclidinium/Formoterol</td><td colspan="2">Volume:</td><td></td></tr>
<tr><td>Name of Active Ingredient:
Aclidinium/Formoterol</td><td colspan="2">Page:</td><td></td></tr>
<tr><td colspan="4">Study Number: LAC-PK-01</td></tr>
<tr><td colspan="4">Title of Report: A Phase 2a, Randomized, Open-label, 2-way Crossover Study to Determine the Pharmacokinetics, Safety, and Tolerability of Aclidinium/Formoterol 400/12 µg Fixed Dose Combination Via Inhaler and Formoterol 12 µg via Foradil® Aerolizer® in Patients with Moderate to Severe Chronic Obstructive Pulmonary Disease</td></tr>
<tr><td colspan="4">Purpose of Study: To evaluate the PK, safety, and tolerability of aclidinium/formoterol fixed dose combination (FDC) 400/12 µg via the Inhaler and formoterol 12 µg via the Foradil® Aerolizer®, both administered BID in patients with moderate to severe chronic obstructive pulmonary disease (COPD).</td></tr>
<tr><td rowspan="2">Date of Report:
17 Apr 2013</td><td colspan="3">Study Period:</td></tr>
<tr><td>From:
January 26, 2012</td><td colspan="2">To:
March 7, 2012</td></tr>
<tr><td colspan="4">Development Phase: 2a</td></tr>
<tr><td colspan="4">Number of Patients:
24 enrolled (24 completed)</td></tr>
<tr><td colspan="4">Design of Study:
Single center, randomized, open-label, 2-way crossover study in a total of 24 male and female patients, at least 40 years of age, with moderate to severe COPD.</td></tr>
<tr><td colspan="4">Clinical Site:</td></tr>
<tr><td colspan="4">Investigator:</td></tr>
<tr><td colspan="4">Formulation(s):</td></tr>
</table>

Mode of Administration: Oral inhalation

Analytical Site.

Statistical Methodology:
Descriptive statistics were provided for all PK parameters for patients who completed the study and had evaluable PK parameters. PK parameters were compared using analysis of covariance. A general linear model (GLM) with sequence, patient within sequence, treatment, and period as factors was used as the basis for the analysis. Statistical inference was based on log-transformed values for the formoterol C_{max} and AUC parameters. The 2-sided 90% confidence interval (CI) for the ratio of geometric means of formoterol C_{max} and AUC between the test and reference treatments were constructed; formoterol T_{max} for the test and reference treatments (without transformation) were compared using the Wilcoxon signed rank test.

Safety parameters (adverse events [AEs], vitals signs, clinical laboratory evaluation, physical examination, and electrocardiographic [ECG] parameters, were summarized for all patients who took at least 1 dose of investigational product.

Methodology:
On 2 occasions, separated by at least 7 days, patients received 1 of the 2 treatments in a randomized order under fed conditions:

Treatment A: Aclidinium/Formoterol 400 µg/12µg FDC, one inhalation twice-daily (morning and evening) for 4 days, then one inhalation (morning) for 1 day via the inhaler

Treatment B: Formoterol 12 µg, one inhalation twice daily (morning and evening) for 4 days, then one inhalation (morning) for 1 day via the Foradil® Aerolizer®

Blood samples were obtained on dosing days (1 to 5 and 12 to 16) at the following time-points: Days 1 and 12 at 0 hour (pre-AM dose), 5 min, 15 min, 30 min and 1, 1.5, 2, 3, 4, 6, 8, and 12 hours (5 minutes before the PM dose) post AM dose; and at 5 and 15 minutes post-PM dose; on Days 2-4 and 13-15 at 0 hour (pre-AM and PM doses) and at 5 min and 15 min (post AM and PM doses); and on Days 5 and 16 at 0 hour (pre-AM dose) and at 5 min, 15 min, 30 min, and 1, 1.5, 2, 3, 4, 6, 8, and 12 hours (post AM dose).

Plasma samples were analyzed for formoterol, aclidinium, LAS34823 and LAS34850 using validated LC-MS/MS methods with good accuracy, linearity, reproducibility, and precision.

Results:
Patient Disposition: Twenty-four male and female patients, with moderate to severe COPD, were enrolled in this study and received at least 1 dose of study medication. All 24 patients completed the study.

Pharmacokinetics - Formoterol:
Mean (CV%) Steady State PK Parameters (N = 24) - PK Analysis Population

Parameter	*Arithmetic Mean A = Foradil 12 µg (N = 24)*	*Arithmetic Mean B = Aclidinium/ Formoterol 400 µg/12µg (N = 24)*	*Ratio of Geometric LS Means %*	*90% CI or p-Value*
$C_{max,ss}$, pg/mL	14.90 (27.9)	16.72 (31.6)	110.75	101.65 - 120.67
$AUC_{0-\tau,ss}$, pg•h/mL	87.14 (27.8)	85.15 (28.3)	97.42	93.71 - 101.27
T_{max}[a], h	0.75 (0.08 - 2.00)	0.08 (0.08 - 2.00)	-	0.0063
$C_{min,ss}$, pg/mL	3.79 (29.8)	3.65 (30.6)	-	-
$C_{avg,ss}$, pg/mL	7.26 (27.8)	7.10 (28.3)	-	-
$T_{½}$, h	8.63 (30.6)	8.23 (25.1)	-	-
λ_z,1/ h	0.09 (27.4)	0.09 (26.2)	-	-
V_z/F, L	1863.98 (42.5)	1809.29 (38.9)	-	-
CLss/F, L/h	147.87 (27.1)	152.42 (28.7)	-	-
PTF%	160.39 (27.1)	186.03 (25.6)	-	-

Rac(C_{max})	1.92 (23.3)	1.85 (29.3)	-	-
Rac(AUC)	2.15 (17.24)	2.04 (11.9)	-	-
Rac(C_{min})	2.66 (21.4)	2.59 (9.82)	-	-

a Median (range) presented

$AUC_{0-\tau,ss}$ = area under the plasma concentration versus time curve over dosing interval at steady state; $C_{avg,ss}$ = average plasma drug concentration over dosing interval at steady state; $C_{max,ss}$ = maximum plasma drug concentration at steady state; $C_{min,ss}$ = minimum plasma drug concentration at steady state; CV% = percent coefficient of variation; CL_{ss}/F = apparent clearance; max = maximum; min = minimum; NA = not applicable; PTF% = peak trough fluctuation over dosing interval at steady state; Rac(AUC) = accumulation ratio calculated from Day 1 and Day 5 AUC estimates; Rac(C_{max}) = accumulation ratio calculated from Day 1 and Day 5 C_{max} estimates; Rac(C_{min}) = accumulation ratio calculated from Day 1 and Day 5 C_{min} estimates; $T_{½}$ = terminal elimination half-life; T_{max} = time of maximum plasma drug concentration; V_z/F = apparent volume of distribution; λ_z = terminal elimination rate constant

Pharmacokinetics - Aclidinium, LAS34823 and LAS34850

Mean (CV%) Steady State PK Parameters for Aclidinium, LAS34823 and LAS34850 (N = 24) - PK Analysis Population

Parameter	***Aclidinium (N = 24)***	***LAS34823 (N = 24)***	***LAS34850 (N = 24)***
$C_{max,ss}$, pg/mL	128.43 (42.1)	149.55 (48.7)	3696.67 (31.9)
$AUC_{0-\tau,ss}$, pg•h/mL	404.25 (47.1)	1206.25 (56.7)	33450.70 (32.0)
$C_{min,ss}$, pg/mL	11.78 (45.5)	65.68 (76.2)	1908.62 (38.8)
$C_{avg,ss}$, pg/mL	33.79 (46.5)	100.52 (56.7)	2787.56 (32.0)
T_{max}[a], h	0.08 (0.08 - 3.00)	1.00 (0.25 - 6.00)	4.00 (1.50 - 8.00)
$T_{½}$, h	4.92 (52.8)	9.48 (45.1)	9.40 (49.5)
λ_z,1/h	0.18 (64.3)	0.08 (33.1)	0.09 (32.1)
V_z/F, L	8227 (72.1)	5579.55 (60.9)	180.80 (58.9)
CLss/F, L/h	1300.03 (66.0)	416.58 (42.0)	13.17 (31.2)
PTF%	385.32 (34.6)	99.8 (27.2)	69.14 (28.3)
Rac(C_{max})	1.38 (35.4)	2.28 (28.1)	1.82 (24.9)
Rac(AUC)	1.95 (28.8)	2.64 (28.6)	2.13 (20.3)
Rac(C_{min})	1.64 (44.7)	3.44 (39.5)	2.45 (32.9)

a Median (range) presented

$AUC_{0-\tau,ss}$ = area under the plasma concentration versus time curve over dosing interval at steady state; $C_{avg,ss}$ = average plasma drug concentration over dosing interval at steady state; $C_{max,ss}$ = maximum plasma drug concentration at steady state; $C_{min,ss}$ = minimum plasma drug concentration at steady state; CV% = percent coefficient of variation; CL_{ss}/F = apparent clearance; max = maximum; min = minimum; NA = not applicable; PTF% = peak trough fluctuation over dosing interval at steady state; Rac(AUC) = accumulation ratio calculated from Day 1 and Day 5 AUC estimates; Rac(C_{max}) = accumulation ratio calculated from Day 1 and Day 5 C_{max} estimates; Rac(C_{min}) = accumulation ratio calculated from Day 1 and Day 5 C_{min} estimates; $T_{½}$ = terminal elimination half-life; T_{max} = time of maximum plasma drug concentration; V_z/F = apparent volume of distribution; λ_z = terminal elimination rate constant

PK Conclusions

Formoterol

Formoterol steady state was achieved following 5 days of twice daily administration, as evidenced by examination of C_{min} values on Days 4 and 5 (less than 10% difference among values). The FDC formulation, lead to an 11% greater formoterol mean $C_{max,ss}$ estimate, as compared to Foradil, with a negligible change in $AUC_{0-\tau,ss}$. However, the 90% CIs of the geometric mean ratios of $C_{max,ss}$ and $AUC_{0-t,ss}$ between the aclidinium/formoterol 400/12ug FDC formulation and Foradil 12ug were within the range of 80% - 125%.

Aclidinium

Aclidinium steady state was achieved following 5 days of twice daily administration, as evidenced by examination of C_{min} values on Days 4 and 5 (less than 10% difference among values). $T_{1/2}$ estimates obtained on Day 1 and at steady state were similar indicating that aclidinium PK is time-independent. Additionally, the accumulation ratio seen following twice daily administration to steady state was consistent with the observed half-life estimate.

Safety/Tolerability

No deaths were reported in this study, and there were no discontinuations due to AEs. Two patients experienced 3 serious adverse events but these were not considered by the principal investigator to be related to the investigational drug product. AEs were generally unremarkable and mild or moderate in severity. Clinical laboratory, vital sign, and ECG monitoring indicated no safety risk associated with oral inhalation of fixed-dose combination of aclidinium/formoterol 400/12 μg and Foradil 12 μg, dosed twice daily for 5 days The most common treatment emergent adverse events (TEAEs) were headache, nausea, gingival pain, application site rash, application site irritation, rhinorrhea and excoriation. There were no clinically significant changes in physical examinations, laboratory findings, vital signs, and ECGs during the study. Overall, both treatments were considered safe and well tolerated by male and female patients with COPD.

Summary and Conclusions