AstraZeneca

Statistical Analysis Plan

Study Code	D6930C00001(PT007001)
NCT #	NCT03364608
Date	13 MARCH 2018

A Randomized, Double-blind, Single dose, Placebo-controlled, 5-Period, 5-Treatment, Crossover, Multi-center, Dose-ranging Study to Compare PT007 to Placebo MDI and Open-Label Proventil® HFA in Adult and Adolescent Subjects With Mild to Moderate Asthma

STATISTICAL ANALYSIS PLAN

Trial Sponsor:	AstraZeneca
Study Number:	D6930C00001 (PT007001)
Study Phase:	II
Product Name:	Albuterol Sulfate Pressurized Inhalation Suspension (AS MDI); PT007
PIND Number:	136213
Indication:	Asthma
Dosage Form/Strength	• AS MDI as o 2 actuations of 45 µg per actuation (90 µg) o 2 actuations of 90 µg per actuation (180 µg)

Protocol Title: A Randomized, Double-blind, Single dose, Placebo-controlled, 5-Period, 5-Treatment, Crossover, Multi-center, Dose-ranging Study to Compare PT007 to Placebo MDI and Open-Label Proventil® HFA in Adult and Adolescent Subjects With Mild to Moderate Asthma

Date of Issue: 13 Mar 2018

Version 1.0

Signed Agreement on Statistical Analysis Plan

FINAL SIGN-OFF SIGNATURES

Study Biostatistician: [redacted]

Peer Review Biostatistician: [redacted]

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse event
ALT	Alanine aminotransferase
AS	Albuterol Sulfate
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
ATS	American Thoracic Society
AUC_{0-6}	Area under the curve from time 0 to 6 hours
AUC_{0-4}	Area under the curve from time 0 to 4 hours
β-hCG	β-human chorionic gonadotropin
BID	Bis in die, twice daily
BMI	Body mass index
BMP	Basic metabolic panel
BPM	Beats per minute
BUN	Blood urea nitrogen
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CI	Confidence interval
CTCAE	Common Terminology Criteria for Adverse Events
DBP	Diastolic blood pressure
DMP	Data Management Plan
CRF	Case report form
DMP	Data management plan
ECG	Electrocardiogram
eCRF	Electronic case report form
eDiary	Electronic diary
eGFR	Estimated glomerular filtration rate
ERS	European Respiratory Society
FEF_{25-75}	Forced expiratory flow from 25% to 75% of FVC
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GGT	Gamma-glutamyl transpeptidase
H_0	Null hypothesis
H_1	Alternative hypothesis
HFA	Hydrofluoroalkane
HR	Heart rate
ICS	Inhaled corticosteroid
ITT	Intention-to-treat
IWRS	Interactive web response system

LABA	Long-acting β2-agonist
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MDI	Metered dose inhaler
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent-to-treat
OTC	Over-the-counter
PDV	Premature discontinuation visit
PCS	Potentially clinically significant
PEFR	Peak expiratory flow rate
PFT	Pulmonary function test
PR	Time from electrocardiogram P wave to the end of the R wave corresponding to electrical systole
QA	Quality assurance
QC	Quality control
QT	Time from electrocardiogram Q wave to the end of the T wave corresponding to electrical systole
QTcF	QT corrected using Fridericia's formula [QT/(RR1/3)]
RR	Time from electrocardiogram R wave to the next R wave corresponding to electrical systole
SAE	Serious adverse event
SABA	Short-acting β-agonist
SAL	Salmeterol
SAP	Statistical analysis plan
sPDP	Statistical protocol deviation plan
SAS	Statistical Analysis System
SBP	Systolic blood pressure
SD	Standard deviation
SI	International System of Units (Système International d'Unités)
SOC	System organ class
TC	Telephone call
TEAE	Treatment emergent adverse event
TP	Treatment period
ULN	Upper limit of normal
US/USA	United States
WHO DDE	World Health Organization Drug Dictionary Enhanced
WHO HD	World Health Organization Herbal Dictionary

1. INTRODUCTION

AstraZeneca is developing a broad range of metered dose inhaler (MDI)-based inhalation aerosols using its porous particle technology platform, including Albuterol Sulfate Pressurized Inhalation Suspension (AS) MDI.

This Statistical Analysis Plan (SAP) outlines the statistical methods for the display, summary, and analysis of data collected within the scope of Clinical Trial Protocol D6930C00001 (PT007001), Version 2.0 (Amendment 1), dated January 12, 2018.

[redacted]

All references to doses of AS MDI and Proventil® HFA (hereafter referred to as Proventil) refer to the albuterol base (i.e., 90 µg albuterol base, which equals 108 µg albuterol sulfate).

2. STUDY OBJECTIVES

2.1 Primary Objective

- To confirm the dose of albuterol delivered from AS MDI that is comparable to Proventil

2.2 Secondary Objective

- To assess the dose response of AS MDI versus Placebo for AS MDI (hereafter referred to as Placebo MDI)

2.3 Safety Objective

- To evaluate the safety and tolerability of AS MDI relative to Placebo MDI and Proventil

3. STUDY ENDPOINTS

3.1 Efficacy Assessments

This is a 5-period, 5-treatment Williams design (Williams 1949). Each Treatment Period will be 1 day, with a Washout Period of 3 to 7 days between Treatment Periods. The day of treatment in each Treatment Period is Day 1. Baseline forced expiratory volume in 1 second (FEV_1) will be calculated using the mean of available pre-dose values on the first day of each Treatment Period (as defined in Section 7.4.3.1).

3.2 Primary Efficacy Endpoint

- Change from baseline in FEV_1 area under the curve from 0 to 6 hours (AUC_{0-6})

3.3 Secondary Efficacy Endpoints

- Change from baseline in FEV_1 AUC from 0 to 4 hours (AUC_{0-4})
- Peak change from baseline in FEV_1

3.4 Other Efficacy Endpoints

- Change from baseline in FEV_1 at each post-dose timepoint
- Time to peak FEV_1
- Percentage of subjects achieving 12% improvement in FEV_1 from baseline within 30 minutes of dose
- Percentage of subjects achieving 15% improvement in FEV_1 from baseline within 30 minutes of dose
- Time to onset of response
- Duration of response

3.5 Safety Endpoints

The safety endpoints include:

- Adverse Events (AEs)/serious adverse events (SAEs)
- Vital signs
- Clinical laboratory parameters
- Electrocardiograms (ECGs)

4. STUDY DESIGN

4.1 Study Design and Plan

This is a randomized, double-blind, single-dose, placebo-controlled, 5-period, 5-treatment, crossover, multi-center study to assess the bronchodilatory effect and safety of 2 dose levels of AS MDI (90 µg and 180 µg) compared with Placebo MDI and open-label Proventil (90 µg and 180 µg) in adult and adolescent subjects with mild to moderate asthma.

This study will be conducted at 10 sites in the US, contributing approximately 7 subjects per site. Across these sites, it is planned that approximately 70 subjects with mild to moderate asthma will be randomized to provide approximately 64 subjects to complete the study.

The sequence of visits is displayed in the Study Flow Diagram (Figure 1).

For more details on the study plan please refer to Protocol Section 4.

Randomization criteria for the study are listed in Section 3.3.1 of Protocol D6930C0001.

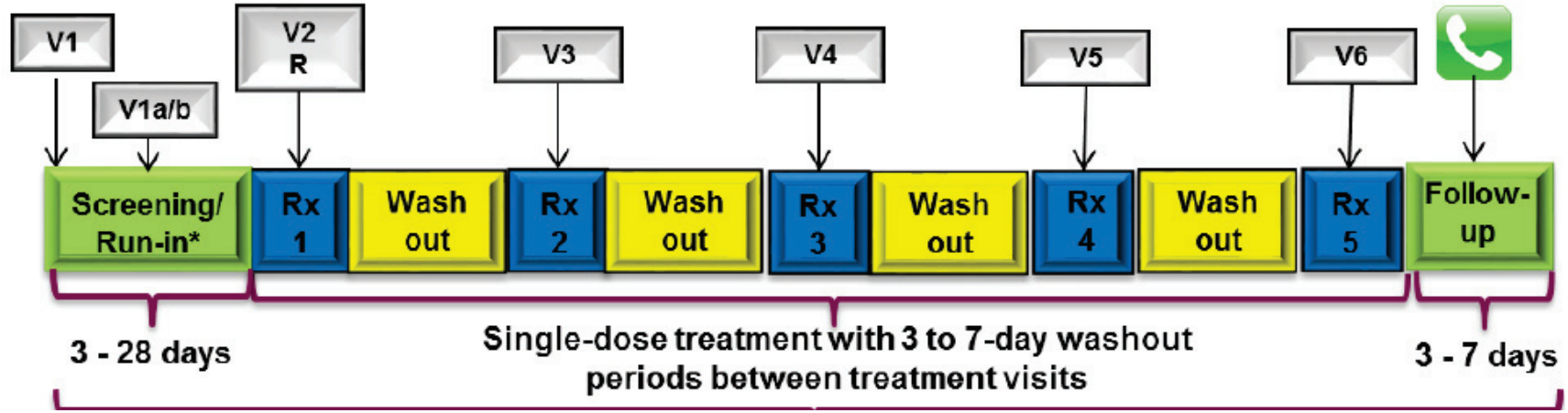
Inclusion criteria for the study are listed in Section 3.1 of Protocol D6930C00001. Subjects eligible for enrollment in the study must meet all of the inclusion criteria. To be eligible, must be at least 12 years of age and no older than 65 years with stable physician-diagnosed asthma for 6 months. Subjects must be on either a SABA as needed as their only asthma therapy or a low to medium ICS dose (either alone or in combination with a LABA) for at least 30 days, as a consistent regimen before screening. Also, subjects must have a pre-bronchodilator FEV_1 between ≥40 and <90% of predicted normal value after withholding SABA for ≥6 hours (and/or Visit 1a and/or Visit 1b, as applicable). Additionally, confirmed FEV_1 reversibility to Ventolin, defined as Post-Ventolin increase in FEV_1 of ≥15% at either Visit 1, Visit 1a, or Visit 1b. Exclusion criteria for the study are listed in Section 3.2 of Protocol D6930C00001. Subjects meeting any of the exclusion criteria are to be excluded from the study. Reasons for exclusion from the study include: chronic obstructive pulmonary disease or other significant lung disease, receipt of oral corticosteroid use (any dose) within 6 weeks of their Visit 1 of the study, and hospitalization for asthma within 6 months of Visit 1.

[redacted].

Detailed schedules for pre- and post-dose procedures to be performed at each study visit are provided in Section 4 of the protocol. A time–and-events schedule is provided below in Table 1.

Visit procedures at each treatment visit (Visits 2, 3, 4, and 5) are provided in Table 2 and at Visit 6 in Table 3.

Figure 1 Study Flow Diagram:



*Subjects on ICS or ICS/LABA prior to Visit 1 will be run-in on Pulmicort Flexhaler 180 or 360 µg BID for a minimum of 14 days.

Abbreviations: BID = twice a day; V=visit; R=randomization; Rx=treatment.

Table 1 Schedule of Events

	Screening Period[a]		Treatment Phase[b]						Follow-up
Treatment Day[a]	Visit 1	Visit 1a/b	Visit 2 Rand. (TP 1) Day 1	Visit 3 (TP 2)	Visit 4 (TP 3)	Visit 5 (TP 4)	Visit 6 (TP 5)	PDV (if Applicable)[c]	TC 3 to 7 days after final dose
	Day -28 to Day -1								
Procedures									
Informed consent (and assent, as appropriate)	X								
Eligibility Criteria	X								
Verify randomization criteria			X						
Verify continued eligibility		X		X	X	X	X		
MDI demonstration/training	X		X	X	X	X	X		
Ventolin reversibility test[d]	X	X							
Medical/surgical history	X								
Demographics	X								
Concomitant medications[e]	X	X	X	X	X	X	X	X[h]	
Spirometry[d]	X	X	X	X	X	X	X		
[redacted]				X	X	X	X		
Physical Examination[f]	X						X	X	
Vital Signs	X		X	X	X	X	X	X	
12-lead ECG	X						X	X	
Pregnancy test[g]	X		X						
Clinical laboratory testing	X						X	X	
Adjust asthma medications per protocol[h]	X	X					X	X	
Randomization			X						
Randomized study drug administered			X	X	X	X	X		
AEs	X	X	X	X	X	X	X	X	X
Telephone contact									X

Abbreviations: AE=adverse event; β-hCG= β-human chorionic gonadotropin; ECG=electrocardiogram; FEV_1=forced expiratory volume in 1 second; ICS=inhaled corticosteroid; LABA= long-acting β2-agonist; MDI=metered dose inhaler; PDV=Premature Discontinuation Visit; Rand.=randomization; SABA= short-acting β-agonist; TC=telephone call; TP=Treatment Period.

Note: When data collection timepoints are concurrent, variables will be collected in the following order: vital signs, ECG, clinical laboratory assessments, and spirometry.

a. Screening Period will be 3 to 28 days for subjects on SABA only before study entry, and 14 to 28 days for subjects on ICS or ICS/LABA before study entry.

b. Subjects to return to clinic within 3 to 7 days following Visits 2, 3, 4, and 5.

c. Subjects who prematurely withdraw from the study will undergo a Premature Discontinuation Visit (see Protocol Section 4.2.5).

d. For subjects who received their regularly inhaled asthma medications and/or SABA on the morning of the visit, spirometry and reversibility will be measured at Visit 1a, which will occur within 10 days of Visit 1. For subjects who do not meet reversibility criteria at Visit 1a, Visit 1b will be scheduled for a second reversibility test, to occur within 7 days. Subjects who do not meet reversibility criteria after the second attempt will be screen failed.

e. At all visits beyond Visit 1, note time of the last dose of asthma medications. The visit must be rescheduled if the last dose of Ventolin was <6 hours before the visit.

f. Includes evaluation of heig[redacted] and weight at Visit 1.

g. A serum pregnancy test (β-hCG) will be performed at Visit 1; urine β-hCG test will be performed before randomization at Visit 2 (for women of child-bearing potential only).

h. At Visit 1, prohibited asthma medications are to be stopped and asthma medications changed as specified in Section Protocol 7.2.2. At the end of Visit 6 (or upon premature discontinuation or screen failure, if applicable), subjects will return to pre-study or other appropriate maintenance asthma medications.

Table 2 Timed Assessments at Visits 2, 3, 4, and 5

	Pre-Dose (minutes)		Post-Dose (minutes)										Before leaving clinic
	-60	-30	5	15	30	45	60	120	180	240	300	360	
Vital signs	X												X
Spirometry	X	X	X	X	X	X	X	X	X	X	X	X	
AEs	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: AE=adverse event.

Table 3 Timed Assessments at Visit 6

	Pre-Dose (minutes)		Post-Dose (minutes)										Before leaving clinic
	-60	-30	5	15	30	45	60	120	180	240	300	360	
Vital signs	X												X
12-lead ECG[b]													X
Spirometry	X	X	X	X	X	X	X	X	X	X	X	X	
Physical examination													X
Clinical laboratory testing													X
AEs	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: AE=adverse event; ECG=electrocardiogram.

4.2 Randomization

Subjects will be randomly assigned to 1 of 10 treatment sequences based on a Williams design (Williams 1949) using an interactive web response system (IWRS). Each sequence will comprise all 5 of the treatments included in this study in a randomized order.

Sequence	Period 1	Period 2	Period 3	Period 4	Period 5
1	A	B	E	C	D
2	B	C	A	D	E
3	C	D	B	E	A
4	D	E	C	A	B
5	E	A	D	B	C
6	D	C	E	B	A
7	E	D	A	C	B
8	A	E	B	D	C
9	B	A	C	E	D
10	C	B	D	A	E

Note: A=Placebo; B=AS MDI 90 µg; C=AS MDI 180 µg; D= Proventil 90 µg; E= Proventil 180 µg.

Randomization will be centralized and stratified by pre-study background therapy consisting of either inhaled corticosteroid (ICS) or non-ICS (subjects not previously treated with ICS).

4.3 Hypothesis Testing

Hypothesis testing will be performed within the context of a linear mixed model analysis, including all treatments. For the primary efficacy comparisons for change from baseline in FEV_1 AUC_{0-6} for the overall population, the primary endpoint, the null hypothesis for each pairwise comparison is that the mean test treatment effect is equal to that of Placebo MDI; the alternative hypothesis is then that the test treatment effect and that of Placebo MDI are not equal. However, while the hypotheses are written for inequality testing, demonstration of superiority relative to placebo is the objective. P-values will be reported as two-sided.

The primary null (H_0) and alternative (H_1) hypotheses with µ representing the mean are:

- H_0: $\mu_{\text{Proventil 180 µg}} = \mu_{\text{placebo}}$
  H_1: $\mu_{\text{Proventil 180 µg}} \neq \mu_{\text{placebo}}$
- H_0: $\mu_{\text{AS MDI 180 µg}} = \mu_{\text{placebo}}$
  H_1: $\mu_{\text{AS MDI 180 µg}} \neq \mu_{\text{placebo}}$

- H_0: $\mu_{\text{Proventil 90 µg}} = \mu_{\text{placebo}}$
  H_1: $\mu_{\text{Proventil 90 µg}} \neq \mu_{\text{placebo}}$
- H_0: $\mu_{\text{AS MDI 90 µg}} = \mu_{\text{placebo}}$
  H_1: $\mu_{\text{AS MDI 90 µg}} \neq \mu_{\text{placebo}}$

The Type I error rate will be controlled at the 5% level (two-sided) across the superiority comparisons of the primary endpoint, FEV_1 $AUC_{0\text{-}6}$. In general, the superiority of Proventil relative to Placebo MDI will be tested first using a dose-ordered approach. If Proventil 180 µg is superior to Placebo MDI, AS MDI 180 µg will be compared to Placebo MDI. If AS MDI 180 µg is superior to Placebo MDI, the superiority of Proventil 90-µg relative to Placebo MDI will be tested. If Proventil 90 µg is superior to placebo, then AS MDI 90 µg will be compared to Placebo MDI.

[redacted]

Comparisons among the dose levels within a product will also be conducted for exploratory purposes. Estimated treatment differences and 95% CIs will be provided.

4.4 Interim Analysis

No interim analyses are planned for this trial.

4.5 Sample Size

Power calculations were based on the properties of the primary endpoint, the change from baseline in FEV_1 $AUC_{0\text{-}6}$. Randomization of 70 subjects in order to achieve at least 64 subjects completing the study will provide >95% overall probability to demonstrate superiority of each treatment relative to Placebo MDI assuming a minimum detectable difference (active–Placebo MDI) of 100 mL, within-subject standard deviation of 115 mL, and two-sided 5% level test. The estimate of the within-subject standard deviation was obtained from a 5-treatment, 5-period dose-ranging study to evaluate albuterol dry powder inhaler and HFA in subjects ages 12 and older with persistent asthma (NCT01058863).

5. DATA AND ANALYTICAL QUALITY ASSURANCE

The overall quality assurance procedures for the study data, statistical programming and analyses are described in Standard Operating Procedures (SOPs) [redacted]). Detailed data management procedures are documented in the study Data Management Plan, Data Validation Check Specifications, and Integrated Safety Data Review Plan. Detailed statistical and programming quality control and quality assurance procedures are documented in the Statistical Analysis and Programming QC/QA Plan.

Transfer of PFT data from the central PFT laboratory [redacted] to Everest will be defined in the [redacted] DMP (Data Management Plan), and data handling rules related to this data are included in Appendix 1 of this SAP. The quality of all PFTs obtained at each timepoint will be graded independently at iCardiac Technologies by qualified personnel. Quality grading assessments will be based on ATS/ERS criteria and will be included in data transfers.

6. ANALYSIS SETS

The following analysis sets are defined in this study.

6.1 Intent-to-Treat (ITT) Analysis Set

The Intent-To-Treat (ITT) analysis set is defined as all subjects who are randomized to treatment and receive at least 1 dose of the study drug. Subjects will be analyzed in each period according to the treatment they were assigned to per the randomization scheme (Note that a subject who used study drug but took less than 1 full dose will qualify for this analysis set).

6.2 Modified ITT (mITT) Analysis Set

A Modified ITT (mITT) analysis set is a subset of the ITT analysis set including subjects who received treatment and have post-treatment efficacy data from at least 2 Treatment Periods. Data judged to be impacted by major protocol deviations will be determined prior to unblinding and excluded per the statistical protocol deviation plan (sPDP). Statistical tabulations and analyses will be by randomized treatment, but data obtained after subjects receive an incorrect treatment will be excluded from the affected periods.

Any evaluability criteria with a potential impact on efficacy results will be defined in an sPDP. The evaluability criteria will be programmatically identified in a blinded fashion aided by a review of data listings prior to database lock. Major protocol deviations (protocol violations), therefore, can result in exclusion of all data from a particular subject from the analysis population or require exclusion of data from a specific timepoint or treatment period and/or subsequent timepoints or subsequent treatment periods for an endpoint(s). Protocol deviations for exclusion of data from the mITT Analysis Set will be agreed by the study team and documented in the blinded data review meeting minutes prior to database lock.

6.3 Safety Analysis Set

The Safety analysis set is defined as all subjects who are randomized to treatment and receive at least 1 dose of the study drug. Subjects will be analyzed according to treatment received rather than per the randomization scheme.

6.4 Not-randomized Analysis Set

The Not Randomized analysis set is defined as subjects who did not receive a randomization number and therefore did not receive a dose of study drug (eg, subjects who were screen failures or stopped participation before being randomized).

6.5 Analysis Sets for Analyses

Analyses will be performed as follows:

Demographics and baseline characteristics will be summarized for the ITT, mITT, Safety, and Not-randomized analysis sets. Extent of exposure will be listed for the Safety analysis set. The Safety analysis set will be used to summarize safety.

Efficacy analyses will be performed for the mITT analysis set. As a sensitivity analysis, the primary endpoint, change from baseline in FEV_1 $AUC_{0\text{-}6}$, will also be analyzed using the ITT analysis set.

7. STATISTICAL ANALYSIS

7.1.1 General Data Handling Rules and Definitions

All data collected on case report forms will be provided in listings, except data collected only for confirmation of study entry criteria and for study administrative purposes. If any randomized subject is found to not have valid documented informed consent, that subject's data will be excluded from the report, except as necessary to document the error.

Except where specified all continuous variables will be summarized with descriptive statistics (the number of non-missing values, mean, standard deviation, median, minimum and maximum) and all categorical variables will be summarized with frequency counts and percentages, by treatment.

Missing data will be maintained as missing in the analysis datasets, unless specified otherwise. For variables where missing data are imputed, another analysis dataset will contain a variable with the imputed value. Thus, the original variable value will be maintained as missing in 1 of the analysis datasets.

All efficacy and safety parameters will be summarized by treatment (unless specified otherwise). Summary statistics for safety will be provided for the Safety Analysis Set, unless otherwise specified.

7.1.2 Data Exclusion and Missing Data Imputation

Pre-dose spirometry values will use the average of the non-missing -60 minute and -30 minute values. A detailed description of the baseline value calculation is in Section 7.4.3.1.

For the mITT analyses, FEV_1 $AUC_{0\text{-}6}$, FEV_1 $AUC_{0\text{-}4}$, and peak FEV_1 will be calculated if there is at least 1 non-missing data point during the first 2 hours post-dose.

Unless otherwise specified, all lung function assessments analyzed that have at least 1 effort that meets ATS/ERS criteria for acceptability will be considered acceptable and contribute to the post-dose assessments. If the PFT assessments at a specific timepoint were deemed to be of unacceptable quality, i.e., none of the efforts met ATS/ERS criteria for acceptability, the PFT assessments obtained at the timepoint will not be included in any efficacy analysis and will be considered missing (Miller et al. 2005). Thus, all observed data will be included in the ITT Analysis Set analysis, with the exception of data at a timepoint which had unacceptable quality based on ATS/ERS criteria.

7.2 Subject Disposition

A disposition table for all screened subjects will be provided *(Table 1.1.1 and Listing 1.2)*. This tabulation will include the number of subjects in each randomized treatment who received study drug, who were withdrawn prematurely, and who completed each treatment. The number of subjects who completed the study will also be provided. The number and percentage of screened subjects who were included in the ITT, mITT, Safety and Not Randomized Analysis Sets will also be tabulated *(Table 1.1.1)*.

A summary of reasons subjects were not randomized, as reported for inclusion/exclusion criteria violated, will be provided for all subjects not randomized (*Table 1.1.2*). A listing of reasons subjects were not randomized will be provided *(Listing 1.4)*. Subjects discontinued from study drug will be withdrawn from the study. Reasons for Premature discontinuation will be summarized for the ITT Analysis Set by randomized treatment *(Table 1.2.1*). The number and percentage of subjects in the mITT and Safety Analysis Sets withdrawn for each reason for withdrawal will be tabulated by treatment actually received *(Tables 1.2.2 and 1.2.3)*.

The number and percentage of randomized subjects who were in each of the analysis sets will be tabulated for each treatment – i.e. for the set of subjects who were randomized to receive the treatment *(Table 1.3)*.

The reason for exclusion from the mITT Analysis Set will be tabulated by study drug for all ITT subjects *(Table 1.4)*. The reasons for exclusion from the ITT and mITT Analysis Sets of a subject or of partial data for a subject will be listed for all randomized subjects, in addition to listing reasons for any subjects to have been excluded from the Safety Analysis Set *(Table 1.1.3)*. A listing of subjects who did not comply with the use of rescue medication and xanthine-containing products (protocol deviations requiring removal of data from the mITT Analysis Set analysis) just prior to spirometry will be provided in *Listing 6.1*. Use of Ventolin HFA (hereafter referred to as Ventolin) at pre-dose or during the post-dose assessments on each specific test day (yes/no), will

be provided in *Listing 6.4*. In addition, the eligibility information (inclusion/exclusion criteria with any waivers granted), of all subjects who are randomized will be listed *(Listing 2).* Subject visits where the stability criteria were not met will be listed *(Listing 6.2)*.

If there are any subjects who took study drug other than what was randomized during the study, both the treatment assigned at randomization and actual treatment(s) received during the Treatment Period will be listed *(Listing 1.3)*. All data listings will show the treatment actually received.

7.3 Demography

The demographic variables are age, gender, race, ethnicity, smoking status (current [a disallowed category], non-smoker, or former smoker), number of years smoked (for former smokers), average number of cigarettes smoked per day (for former smokers), number of pack years smoked (for former smokers), and prior asthma treatment regimen (SABA prn use only, ICS, ICS/LABA). The physical characteristics variables are weight, height, and BMI (body mass index). The data handling rules for age, BMI, and number of pack years smoked are described in Appendix 1.

Subject demographics and smoking status/history will be summarized for the mITT, ITT, and Safety Analysis Sets and for Non-Randomized subjects *(Tables 1.5.1 through 1.5.4, respectively, and Listing 1.2)* for all subjects.

7.3.1 Asthma History, Screening/Baseline Spirometry, and Reversibility

The number of months since the date of the diagnosis of asthma as shown on the Screening Visit 1 eCRF, and determined relative to the first dose of study drug in the study (Appendix 1) will be summarized for the mITT and Safety Analysis Sets *(Tables 1.6.1 through 1.6.2 respectively, and Listing 4.1)*. The screening and baseline spirometry variables FEV_1, FEF_{25-75}, and FVC will be summarized separately for Visit 1 and Visit 2 *(Tables 1.7.1 and 1.7.2, respectively, for the mITT and ITT Analysis Sets, and Listing 6.4)*. For this purpose, Visit 1 will be Visit 1, 1a, or 1b, whichever visit had the highest FEV_1 result post-dose.

Per Protocol Section 4.1, reversibility to Ventolin (SABA) will be evaluated at Visits 1, 1a (if needed), or 1b (if needed) and defined as:

- The comparison of the best FEV_1 effort obtained at 30 minutes pre-bronchodilator to the best FEV_1 effort obtained at 30 minutes post-bronchodilator following administration of Ventolin. A subject is considered reversible to Ventolin if the improvement in FEV_1 at 30 minutes post-Ventolin is ≥15%.

See Appendix 1 for data handling rules and the formula for determination of reversibility variables.

Reversibility to Ventolin at Screening will be summarized for the mITT and ITT Analysis Sets and listed *(Tables 1.8.1 and 1.8.2, respectively, and Listing 3).* Also included will be a summary of the change in FEV_1 from pre-bronchodilator to post-bronchodilator.

7.3.2 Medical and Surgical History at Screening, Pregnancy Testing at Screening and Baseline

Medical history at Screening will be coded using the version of the Medical Dictionary for Regulatory Activities (MedDRA) that is current at the time of data base lock.

Medical and Surgical History at Screening will be summarized by actual treatment for the Safety Analysis Set and listed for all randomized subjects *(Table 1.9 and Listing 4.2)*.

Pregnancy Testing Results from Screening and Baseline will be listed *(Listing 4.3).*

7.3.3 Prior, Concomitant, and Post-Treatment Medications/Treatments

All prescription and over-the-counter (OTC) medications, as well as any herbal or vitamin supplements, taken by the subject within 30 days of Visit 1 will be recorded on the Prior and Concomitant Medications eCRF page. All concomitant medications taken during the study will be recorded on the Prior and Concomitant Medications eCRF page.

Coding: Verbatim medication/treatment terms coded by [redacted] will be assigned a preferred term and an ATC (anatomic therapeutic chemical class) term using the latest version of the World Health Organization Drug Dictionary Enhanced and World Health Organization Herbal Dictionary (WHO DDE and WHO HD) available (Version: Q3; 2017 or later).

Multiple ATC Assignments: If there are multiple ATC codes assigned to the same concomitant medication, the "primary" one based on an AstraZeneca medical evaluation will be used.

Additional details for the definition of **Prior medication/treatment, Concomitant medication/treatment,** and **Post-Treatment medication/treatment** are described in Appendix 1.

Concomitant asthma and non-asthma related medications/treatments will be summarized by preferred term and actual treatment received for the Safety Analysis Set separately during the Treatment and Washout Periods *(Tables 1.11.1a, 1.11.1.b, 1.11.2a, and 1.11.2b)*. Prior, concomitant, and post-treatment medications will be displayed in separate listings for Asthma and Other medications *(Listings 4.4 and 4.5, respectively)*.

Reported prior medication for asthma and other indications will be tabulated for all subjects *(Tables 1.10.1 and 1.10.2)* and listed separately *(Listings 4.4 and 4.5, respectively)*.

Ventolin or Pulmicort dispensing will be listed *(Listing 5.1.2).*

7.3.4 Extent of Exposure to Study Drug

A listing of treatment dosing information will be provided in Listings 5.1.1 and 5.2. Any comments related to study drug or any other study comments will be listed (Listing 9.3).

7.4 Efficacy Analyses

Reasons for missed visits (asthma-related or not) for each subject will be listed *(Listing 6.3)*. Spirometry measurements will be listed *(Listing 6.4)*.

7.4.1 Primary Efficacy

7.4.2 Study Day

Study day is defined relative to the date of the first study drug administration. Within-period study day, or day of assessment/event, is defined relative to the date of study drug within the period. Additional definitions are provided in Appendix 1. Handling of unscheduled visits for efficacy endpoints is discussed in Section 7.4.3.3.

7.4.3 Time Points and Time Intervals for Efficacy Endpoints

The definitions of several terms related to time points and time intervals for efficacy endpoints are given in this section.

7.4.3.1 Baselines for Analysis

Since pre-dose values are known to be variable and an isolated timepoint may not accurately reflect the true baseline, the following baseline will be used for the statistical analyses of study assessments unless otherwise specified: the mean of available pre-dose values on the first day of each treatment cycle, i.e., the mean of pre-dose values at Visits 2, 3, 4, 5, and 6, where the mean of the 60- and 30-minute pre-dose value for each visit is obtained and then the visit means are averaged.

7.4.3.2 Change from Baseline

Change from baseline denotes the value at a timepoint minus the value at baseline, where baseline was defined in the previous subsection.

7.4.3.3 Handling of Unscheduled Visits:

Data from unscheduled visits will not be used for efficacy analyses, but will be listed *(Listing 6.4)*.

7.4.3.4 Time Windows for Spirometry Assessments

All available data with the actual timepoints (versus nominal timepoints) will be used for AUC calculations, determination of peak change from baseline in FEV_1, re sponders analyses, onset of response, and offset of response. Time windows will apply only to the change from baseline in FEV_1 by-timepoint analysis.

[redacted]

[redacted] [redacted]

[redacted]	[redacted]	
	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

7.4.4 Primary Efficacy Analysis

The primary objective of this study is to confirm the dose of albuterol delivered from AS MDI that is comparable to Proventil.

The FEV_1 $AUC_{0\text{-}6}$ is the area under the curve for the change from baseline in FEV_1 calculated using the trapezoidal rule. All observed data will be utilized with the trapezoidal rule to calculate

AUC. For the purpose of AUC calculations, the value of the spirometry parameter at time 0 will be the change from baseline in pre-bronchodilator FEV_1 at the visit. To aid in interpretation, all AUC values will be normalized by dividing the AUC by the time from the first to the last non-missing value (typically 6 hours). If AUC is based on just one 1 assessment (i.e., a change from baseline value), that change from baseline value will be the value of the AUC (the trapezoidal rule and normalization will not apply as the area is 0 and the time interval is 0).

The FEV_1 AUC_{0-6} will be analyzed using a linear mixed model with a random subject effect. The fixed effects in the model will include treatment, treatment sequence, baseline FEV_1, and period. An ICS use subgroup analysis will be based on a linear mixed model with covariates of treatment, treatment sequence, baseline FEV1, period, ICS Use subgroup (ICS use at Screening and Did not use ICS at Screening), and treatment-by-subgroup interaction.

The least squares (LS) mean and the standard error of this mean with the corresponding two-sided 95% confidence interval will be provided for each treatment based on the overall study population and then separately within each of the 2 ICS subgroups. The estimated treatment differences and 95% CIs will be provided for all treatment comparisons based on the overall study population, and then separately within each of the 2 ICS Use subgroups.

Superiority comparisons of AS MDI relative to Placebo MDI and Proventil versus Placebo MDI will be conducted first using a dose-ordered approach. A two-sided alpha level of 0.05 will be employed. Estimated treatment differences and 95% confidence intervals (CIs) will be provided for the superiority comparisons. As described in detail in Section 4.3, the superiority of Proventil relative to Placebo MDI will be tested first using this dose-ordered approach. If Proventil 180 µg is superior to Placebo MDI, AS MDI 180 µg will be compared to Placebo MDI. If AS MDI 180 µg is superior to Placebo MDI, the superiority of the Proventil 90-µg dose relative to Placebo MDI will be tested. If Proventil 90 µg is superior to placebo, then AS MDI 90 µg will be compared to Placebo MDI.

[redacted].

Comparisons among the dose levels within a product and comparisons within the ICS Use subgroups will be conducted for exploratory purposes. Estimated treatment differences and 95% CIs will be provided.

The primary analysis will be conducted using the mITT Analysis Set. Supportive analyses for the primary endpoint will be performed using the ITT Analysis Set. Assumptions underlying the primary analysis will be evaluated and additional analyses may be performed (see Section 7.4.7).

Summary statistics and the results of statistical testing for the primary endpoint will be provided in *Table 2.1.1* by treatment overall and for each subgroup for the mITT Analysis Set and in *Table 2.1.2* for the ITT Analysis Set.

7.4.5 Secondary Efficacy

The secondary endpoints will be analyzed using a similar approach as that of the primary endpoint. Linear mixed models will be fit with a random subject effect. The fixed effects in the model will include baseline FEV_1, treatment, treatment sequence, and period.

The FEV_1 AUC_{0-4} will be calculated in a similar manner as FEV_1 AUC_{0-6}; however, the trapezoidal rule will only be implemented through the 4-hour nominal timepoint. The AUC values will be normalized accordingly.

The peak change from baseline in FEV_1 will be calculated using the largest FEV_1 value measured during the 6 hours post-dosing.

Secondary efficacy endpoints will be analyzed using the mITT Analysis Set. Tables and figures will be as follows:

- Change from baseline in FEV_1 AUC_{0-4}: *Table 2.2.1 for the mITT Analysis Set*.
- Peak change from baseline in FEV_1: *Table 2.2.2 for the mITT Analysis Set*.

7.4.6 Other Efficacy

Change from baseline in FEV_1 at each post-dose timepoint will be presented graphically by treatment and will be analyzed using a linear mixed model with a random subject effect. The fixed effects will include treatment, time point, treatment-by-time point interaction, treatment sequence, baseline FEV_1, and period. The covariance within subject-periods will be unstructured over the time points. Note that the sample sizes (N) at 180- and 300-minutes post-dose will be smaller than the remaining timepoints due to adjustment to the spirometry assessment schedule outlined in Version 2 of the protocol (See Section 8).

The median values for time to peak FEV_1 will be reported by treatment. The median differences and corresponding Hodges-Lehmann 95% CIs will be presented for pairwise comparisons among the treatments.

The percentages of subjects achieving a 12% and 15% improvement from baseline within 30 minutes post dose will be tabulated by treatment. Responders will be defined as subjects achieving $\geq$15% (or $\geq$12%) improvement in FEV_1 within 30 minutes after dosing. The odds of being a responder will also be estimated using a generalized mixed effects model with fixed effects of treatment and period, and a random subject effect.

The time to onset of response for each individual subject will be defined as the first timepoint for which an increase from baseline FEV_1 of at least 15% (or 12%) is observed within the first 30 minutes post dose. The median time to onset of response will be reported by treatment. The

median differences and corresponding Hodges-Lehmann 95% CIs will be presented for pairwise comparisons among the treatments (Han L, Paper ST-154). Only subjects who achieved the 15% (or 12%) improvement within the first 30 minutes post dose will be included in this analysis.

The duration of response for each subject will be defined as the time from onset of at least a 15% (or 12%) increase in FEV_1 to the offset of the 15% (or 12%) increase in FEV_1 relative to baseline. If offset of response was not achieved during the assessment period, the last available time of assessment will be used as the offset. If a subject had a 2nd onset of response subsequent to achievement of offset, their data for that period will be excluded from the duration of response analysis. Descriptive statistics including the N, arithmetic mean, standard deviation, median, minimum, and maximum for duration of response will be reported by treatment. The duration of response will be analyzed using a linear mixed effects model similar to that of the primary endpoint or a distribution-free method (Hodges-Lehmann) as appropriate to the data. As an additional sensitivity analysis to assess potential bias imposed by the limited spirometry sampling scheme of protocol Version 1.0, the duration of response analysis will be repeated excluding those subjects who are missing the 180- and 300-minute post timepoints.

The other efficacy endpoints will be analyzed using the mITT Analysis Set. Tables and figures will be as follows.

- Change from Baseline in FEV_1 at each post-dose timepoint: *Table 2.3.1 and Figures 2.3.1.1 and 2.3.1.2 for the mITT Analysis Set.*
- Time to peak FEV_1: *Table 2.3.2 for the mITT Analysis Set.*
- Percentage of subjects achieving 12% improvement in FEV_1 from baseline within 30 minutes of dose: *Table 2.3.3 for the mITT Analysis Set.*
- Percentage of subjects achieving 15% improvement in FEV_1 from baseline within 30 minutes of dose: *Table 2.3.3 for the mITT Analysis Set.*
- Time to onset of response: *Table 2.3.4 and Table 2.3.5 for the 12% Improvement in FEV_1 and the 15% Improvement in FEV_1, respectively, for the mITT Analysis Set.*
- Duration of response: *Tables 2.3.6, 2.3.7, 2.3.8, and 2.3.9 for the 12% Improvement in FEV_1, 12% Improvement in FEV_1 in subjects who have assessments at the 180- and 300-minute post-dose timepoints, 15% Improvement in FEV_1, and 15% Improvement in FEV_1, in subjects who have assessments at the 180- and 300-minute post-dose timepoints, respectively, for the mITT Analysis Set.*

7.4.7 Data Validation and Transformation

In general, the distribution of spirometry measures is well approximated by a normal distribution. Under some circumstances, however (eg, during an exacerbation unrelated to treatment), extreme and atypical values can arise. Such values have high influence on estimation of variance parameters and on standard errors of fixed effect estimates. The distribution of scaled marginal residuals, and influence statistics will be examined to identify such cases. In the event that a single or small number of such outlying values are found to exist and found to be highly influential, the

effects may be ameliorated by either transformation or removal of the outlier. Transformations to be considered may include the logarithmic transformation or normal rank transformations. Where outliers are removed, sensitivity analyses including those values will be reported.

The assumption of normality in the primary, secondary, and other efficacy endpoints, Change from Baseline in FEV_1 AUC_{0-6}, Change from Baseline in FEV_1 AUC_{0-4}, Peak change from baseline in FEV_1, and duration of response will be checked by visually inspecting the distribution of the scaled (decorrelated) residuals. Also, model fit and the assumption of homogeneity of variance among treatments will be verified by inspection of scatter plots of predicted vs. residuals, residuals vs. treatment, and by box plots of residuals for treatment. Plots for scaled (marginal) residuals will be prepared using option=VCIRY on the model statement and the ODS graphics option. If the assumption of homogeneity does not hold (sample variances appear heterogeneous), then the final model will be fit with an UN or CSH covariance structure. (Appendix 3).

Changes in spirometry measures from baseline, and from timepoint to timepoint will be examined graphically before database lock, and before unblinding, as part of data quality management.

7.5 Safety Analyses

All safety analyses are based on Safety Analysis Set. Hypothesis testing will not be performed for any safety analyses. No formal statistical analysis of safety data is planned. Safety data will be summarized by treatment and listed.

7.5.1 Adverse Events

Adverse events will be collected and coded using the latest version (20.1 or later) of the MedDRA available. A glossary of MedDRA preferred terms used for AEs reported in the study along with the associated Investigator's verbatim will be provided in Listing 7.2. The version of MedDRA current at the time of database lock will be used for the final analysis of data.

Adverse events occurring from the time the subject signs informed consent until the subject is randomized will be summarized as medical history and not as an AE unless the event meets the definition of an SAE as defined in Protocol Section 6.2.

An adverse event is considered treatment-emergent if the date of onset is on or after the date of first dose of study drug in the study. An AE would be considered attributable to a treatment (corresponding to a treatment period or washout or final follow-up period) if the onset of the AE was during a treatment period (or washout period or final follow-up period). Should there not be sufficient information to determine during which period that an AE started, the AE will be counted as having occurred in all treatment periods (and washout periods or final follow-up period) prior to the end date of the AE if this is reported as long as the subject received study drug during those treatment periods. If both start and end date of an AE are unavailable, the AE will be counted in all treatment periods prior to the date of last contact on the End of Treatment eCRF (including the treatment taken on the day of the last contact) as long as the subject received study drug during those treatment periods. Any AE with onset after the last treatment in the study will be attributed to this last treatment. Adverse events after the Follow-up Telephone Call scheduled 3-7 days after

Visit 6 or a discontinuation visit will not be considered treatment-emergent, but will be listed in adverse event data listings.

Counting Rules for Adverse Events with Onset in a Treatment Period or Washout Period (or Follow-up Period):

1. A subject with more than 1 different AE in a particular system organ class (SOC) will be counted only once in the total of subjects experiencing AEs in that particular SOC.
2. A subject having experienced the same event (AE preferred term) more than once will be counted only once in the number of subjects with that event.

Events with Irregular Start Dates: All adverse events will be included in the tabulations regardless of the completeness of the onset dates.

Missing/incomplete (partial) AE start and end dates will not be imputed for data listings.

Both the treatment and the washout periods include treatment with Pulmicort Flexhaler if subjects were previously on an ICS prior to the start of the study. Additionally, the washout periods included treatment with Ventolin. AEs reported as starting during a Washout Period or the final follow-up period will be excluded from the main analyses of AEs. As a supportive analysis, AEs will be assigned to the last randomized treatment received including those occurring during the Washout Period (*Table 3.2.2 for AEs and Table 3.6.2 for SAEs*).

All adverse events, whether treatment-emergent or not, will be included in the listings. Reported adverse events by system organ class, preferred term, treatment, center, subject, and onset day will be provided (*Listing 7.1*). Reported adverse events by treatment, center, subject, and onset date will also be provided (*Listing 7.3*).

The listing of adverse events will provide the severity, maximum severity, relationship to study drug, action taken and outcome for each adverse event. Any SAEs reported will be listed (*Table 3.7.1 for the treatment period analysis not including the washout and follow-up period and Table 3.7.2 for the analysis including all AEs including those with onset during the washout or follow-up period after the treatment period)*. Suspect drug assessment data associated with an SAE (collected on the Suspect Drug Assessment CRF) will be listed by SAE (*Listing 4.6*). Adverse events leading to discontinuation of study drug will be listed *(Table 3.5)*. A listing of any reported deaths during the study will be provided (*Table 3.10*); the study drug taken most recently prior to the death and the number of days since the dose of this study drug at the time of the death will be included in the listing.

An overview summary table will be prepared. The table will provide the incidences of subjects, for all subjects and for each treatment, with the following: at least 1 treatment-emergent adverse event, at least 1 treatment-emergent related adverse event, at least 1 treatment-emergent serious adverse event, at least 1 treatment-emergent serious related adverse event, at least 1 treatment-emergent adverse event leading to study drug discontinuation and premature study withdrawal, and

a report of death *(Table 3.1.1, washout TEAEs excluded).* As a supportive analysis, AEs will be assigned to the last randomized treatment received including those occurring during the washout period or the final follow-up period *(Table 3.1.2).*

The incidence of an adverse event (AE) for a treatment will be defined as the number and percent of subjects experiencing an event attributable to that treatment. For each group, the following will be prepared for each treatment and for overall, for each primary system organ class, and for each preferred term within a system organ class:

1. The incidence of all treatment-emergent adverse events *(Table 3.2.1)*
2. The incidence of non-serious treatment-emergent adverse events occurring in ≥5% of subjects in a treatment *(Table 3.2.4)*
3. The incidence of all treatment-related treatment-emergent adverse events *(Table 3.3)*
4. The incidence of treatment-emergent adverse events leading to study drug discontinuation *(Table 3.4)*
5. The incidence of treatment-emergent serious adverse events *(Table 3.6.1)*
6. The incidence of treatment-emergent serious related adverse events *(Table 3.8)*
7. The incidence of all treatment-emergent adverse events by highest severity *(Tables 3.9.1-3.9.5).* There will be a separate table for each treatment.
8. The incidence of treatment-emergent adverse events occurring in at least 2% of subjects in any treatment (*Table 3.2.3*, sorted by descending frequency of events in a preferred term).

7.5.2 Clinical Laboratory Data

Clinical safety laboratory tests will be collected at Visit 1, Visit 6 (post-dose) and during a Premature Discontinuation Visit, if applicable. Laboratory tests will be analyzed by a central laboratory according to standardized, validated assays. The following clinical laboratory parameters that will be assessed are noted in Table 5.

Table 5 Lab Parameters

Hematology	
Hemoglobin	Mean corpuscular hemoglobin (MCH)
Hematocrit	Mean corpuscular hemoglobin concentration (MCHC)
White Blood Cell count with differential	Mean corpuscular volume (MCV)
Red Blood Cell count	
Platelet Count	
Clinical Blood Chemistry	
Liver Enzyme and Other Function Tests	**Other Clinical Blood Chemistry**
Alanine aminotransferase (ALT)	Albumin
Aspartate aminotransferase (AST)	Blood urea nitrogen (BUN)[a]
Alkaline phosphatase	Calcium[a]

Bilirubin, total	Chloride[a]
Gamma-glutamyl transferase	Cholesterol
	Bicarbonate
	Creatinine[a]
	Glucose[a]
	Magnesium
	Potassium[a]
	Phosphate
	Protein, total
	Sodium[a]
	Triglycerides
	Urea

Other Tests:

Pregnancy test (women of child-bearing potential only): serum (human chorionic gonadotropin [hCG]) at Visit 1, and urine HCG before randomization at Visit 2, as detailed in Table 1

Creatinine clearance will be estimated by the central laboratory at Screening only using eGFR (estimated glomerular filtration rate) using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) published formula.

[a] Parameters included in the Basic Metabolic Panel (BMP).

Clinically Significant Laboratory Abnormalities as identified by the investigator after the start of study drug will be recorded as an Adverse Event and tabulated as an AE in the AE analysis. Abnormalities occurring prior to the start of treatment will be noted in medical history and presented in a data listing. Per protocol, the criteria for a "clinically significant" laboratory abnormality are:

a. A laboratory abnormality that leads to study drug dose suspension or discontinuation
b. A laboratory abnormality that results in any therapeutic intervention (i.e., concomitant medication or therapy)
c. Any other laboratory abnormality judged by the Investigator to be of any particular clinical concern (eg., significant fall in hemoglobin not requiring transfusion)

For laboratory abnormalities that do not meet the above criteria but are outside of the normal reference range, the investigator should indicate whether the value is clinically significant or not clinically significant for the subject.

All laboratory data will be stored in the database with the units in which they are originally reported. Laboratory data in subject data listings will be presented in the International System of Units (SI units; Système International d'Unités) where available. Laboratory data not reported in SI units will be converted to SI units before further processing or data analysis. Individual clinical laboratory variables for hematology and clinical chemistry, including creatinine clearance (eGFR), will be provided in listings *(Listing 8.1 for central laboratory hematology, Listing 8.2 for central*

laboratory blood chemistry and kidney function, and Listing 9.3 for pregnancy test results after the start of treatment). Comments for central laboratory testing will be listed *(Listing 8.3)*. For listings, laboratory values will be flagged as Low or High based on the reference ranges provided by the central laboratory, Covance. These flags along with the reference ranges will be provided in the laboratory data listings.

7.5.3 Vital Signs

A **Clinically Significant Abnormality** in vital signs identified by the investigator will be recorded as an Adverse Event if it occurs after the start of treatment. These adverse events will be included in the AE summaries; abnormalities prior to the start of treatment will be noted in medical history and listed.

Potentially clinically significant changes in systolic blood pressure (SBP), diastolic blood pressure (DBP), and Heart Rate will be defined based on the following criteria provided by AstraZeneca:

Table 6 Potentially Clinically Significant Criteria for Systolic and Diastolic Blood Pressure Parameters and Heart Rate

Parameter (mmHg)	Post-Baseline Criteria
SBP, increase	≥180 and increase from baseline ≥20
SBP, decrease	≤90 and decrease from baseline ≥20
DBP, increase	≥105 and increase from baseline ≥ 15
DBP, decrease	≤50 and decrease from baseline ≥ 15
Tachycardia Event	≥ 110 bpm and increase ≥ 15% from baseline
Bradycardia Event	≤ 50 bpm and decrease ≥ 15% from baseline

Vital signs, height, weight, BMI, SBP, DBP, and Heart Rate will be listed *(Listing 9.1)*.

Baseline is defined as the last pre-dose measurement taken prior to dosing on Day 1 of a treatment period.

Change from baseline for a timepoint of a Treatment Period is defined as the vital sign value for the timepoint minus the baseline value.

For summaries by timepoint, the latest vital sign value (in the case of multiple values) for a scheduled post-baseline timepoint on a scheduled visit for a Treatment Period will be employed.

Descriptive statistics (mean, median, standard deviation, and range) for change from baseline will be tabulated by vital sign parameter and treatment for each scheduled assessment time.

Summary statistics (n, mean, median, standard deviation, minimum and maximum) of scheduled pre-dose and post-dose values as well as changes from baseline for each vital sign parameter will be tabulated by treatment *(Table 3.11.1)*. Values will not be allocated across Treatment Periods.

7.5.4 Electrocardiogram (ECG)

A **Clinically Significant Abnormality** for a 12-Lead ECG measurement identified by the investigator as a clinically significant abnormality will be recorded as an Adverse Event if it occurred after the start of study drug. These adverse events will be included in the AE summaries.

The ECG parameters that will be assessed include heart rate (HR), RR interval, PR interval, QRS axis, QRS interval, QT interval, and QTcF (Fridericia's Formula) interval. The QTcF (Fridericia Corrected QT) is defined as $[QT/(RR^{1/3})]$.

All 12-Lead ECG measurements for the Safety Analysis Set will be listed *(Listing 9.2)*.

7.5.5 Physical Examination

Any physical examination abnormality reported after the start of treatment for a subject is to be reported as an adverse event and included in the AE summaries.

8. CHANGES FROM METHODS PLANNED IN THE PROTOCOL

The protocol was amended on 12 January 2018 to include spirometry assessments (180 and 300 minutes post-dose) that were inadvertently omitted from Version 1 of the protocol. Subjects randomized after this amendment have spirometry assessments at 180 and 300 minutes in addition to the timepoints outlined in Version 1 of the protocol, [redacted]. All subjects will be included in the efficacy analyses irrespective of their spirometry sampling scheme.

The protocol specified that the baseline for vital signs analyses would be the average of the vital sign values taken prior to dosing on the day of randomization. Since multiple values were not scheduled to be collected at randomization and since each treatment visit had vital signs measurements taken prior to dosing (under the condition that restricted asthma medications were not to be taken within 6 hours of test day assessments), the baseline for vital signs has been updated as follows: Baseline is defined as the last pre-dose measurement taken prior to dosing on Day 1 of a treatment period.

9. STATISTICAL SOFTWARE

Data processing, statistical screening, descriptive reporting, and analysis of the efficacy and safety data will be performed using SAS (Version 9.4 or higher).

10. REFERENCES

Miller et al 2005. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. Eur Respir J 2005;26(2):319-338.

Han L, Calculating the point estimate and confidence interval of Hodges-Lehmann's median using SAS® software. Southeast SAS® Users Group (SESUG) 2008; Paper ST-154.

APPENDIX 1 DATA HANDLING RULES

Programming of the tables, listings and figures will be performed using SAS Version 9.4 or a more recent version. The following table presents algorithms (not stated elsewhere) to be used in SAS to calculate the derived variables, including rules for handling missing data or partial dates, or irregular/unexpected data issues.

Category	Description	Data Handling Rules
Pulmonary Function Testing Data	[redacted] data transferred	• Only data of rank =1 (best effort) will be transferred; data transferred will be grade 1 = acceptable, grade 2 = borderline, or grade = 3 (unacceptable). Only data of grade = 1 or grade = 2 will be included in baseline or on-treatment spirometry calculations. • All data transferred from [redacted]. (grade = 1, 2, or 3) will be listed in data listings with the grade.
Age (years)	Age (years)	Age = integer part of ((Visit 1 date – Birth date + 1)/365.25)
Smoking History	Number of pack years smoked	Number of pack years smoked = (number of cigarettes per day/20) x number of years smoked. It is zero if the number of years smoked is zero or if the subject is a non-smoker.
BMI	Body Mass Index	BMI = (weight(kg))/(height(cm)/100)^2
Asthma History	Months Since Diagnosis	Months Since Diagnosis = (Date of First Dose of Study Drug in the study – Date Asthma First Diagnosed)/30.475.
	Missing Date Asthma First Diagnosed	Day of Diagnosis will be imputed for all subjects as the 1st of the month.
	Missing month of Date Asthma First Diagnosed	Missing month of Diagnosis will be imputed as June, or the month in which 1st will be the latest before informed consent date, whichever is earliest.
Medical History	Medical History Begin Date of Condition	Missing month of Condition will be imputed as June, or the month in which 1st will be the latest before informed consent date, whichever is earliest. Begin date of Condition will be imputed for all subjects as the 1st of the month.

Category	Description	Data Handling Rules
	Medical History End Date of Condition	Other than for 'Ongoing' conditions, missing month of End Date of Condition will be imputed as June, or the month in which 1st will be the latest before informed consent date, whichever is earliest. End date of Condition will be imputed for all subjects as the 1st of the month.
Surgical History	Surgical History Date of Surgery	Missing month of Surgery will be imputed as June, or the month in which 1st will be the latest before informed consent date, whichever is earliest. Begin date of Surgery will be imputed for all subjects as the 1st of the month.
Screening Reversibility	Screening Percent Reversibility	The screening percent reversibility to Ventolin is 100 x [post-Ventolin FEV_1 – pre-Ventolin FEV_1)]/ [pre-Ventolin FEV_1]. For this definition, "post-Ventolin FEV_1" and "pre-Ventolin FEV_1" are the best effort values obtained after the dose of Ventolin and before the dose of Ventolin, respectively.
First and Last Treatment Dates	Date/time of first dose of the first study drug taken in the study and the date/time of the last dose of the last study drug taken in the study.	The date and time (24 hr. clock) of the dose of study drug will be taken from the Study Drug Administration eCRF. The time of the last dose of study drug will be the last time of dosing from the [redacted] dataset.
Last Visit Date	Date of Last Visit	Date of last Visit according to the Visit eCRF.
Last Study Participation Date (STDM variable, RFPENDTC)	Last Study Participation Date (STDM variable, RFPENDTC)	Last study participation date is defined as last known date of contact which would be the later of the following dates: last visit date, date of the last dose, date of last contact if lost-to-follow-up, date of telephone follow-up, or death date.
Study Day Definitions	**Study Day** for assessment/event which occurs on or after the date of a study drug	Study Day = Date of assessment/event – date of the dose of study drug + 1.
	Within-Period Study Day for an on-treatment assessment/event study	Within-Period Study Day = Date of assessment/event – date of dose of study drug within the respective Treatment Period + 1.

Category	Description	Data Handling Rules
	drug	
	Study Day for assessments/events on days prior to the dose of the first study drug in the study	Study Day = date of assessment/event - dose date of treatment in the study.
	Study Day Post-Treatment of Assessment or event which occurs after a study drug	Study Day = 'P' concatenated with the number of days post-treatment that the assessment or event occurred which is defined as Date of assessment/event – date of dose of study drug in the last period (i.e. most recent treatment).
	Study Day of Randomization	Study Day of Randomization = date of randomization – date of the first dose of study drug in the study if date of randomization is before date of first dose of study drug. Study Day is 1 if the day of first study drug in the study is on the day of randomization.
	First Dose Date	**First Dose Date** in the study is defined as the date of the first dose of study drug in the study.
	Last Dose Date	**Last Dose Date** in the study is defined as the date of the last dose of study drug in the study (defined as the last date of dosing from the Study Drug Administration eCRF).
	Last Study Day	**For subjects who did not receive study drug in the study (e.g., Non-Randomized Subjects)**, Last Study Day is defined as (the later of the last visit date or the date of last contact for subjects lost-to-follow-up from the End of Treatment eCRF) – Date of Screening Visit + 1. **For subjects who received study drug in the study,** Last Study Day is defined as (the later of the last visit date or the date of last contact for subjects lost-to-follow-up from the End of Treatment eCRF) – first dose date in the study + 1.

Category	Description	Data Handling Rules
	Days Since Last Dose for event (e.g., Death)	**Days Since Last Dose** is defined as date of event – date of last dose of study drug.
	Treatment Day	Treatment Day 1 is the study day of the dose of a study drug.
Treatment Period	Treatment Period	A treatment period for a treatment is the date of the dose of the treatment (Treatment Day 1 of a treatment)
Duration of Event	The duration of any event (not including duration of asthma)	The duration of any event is defined as (stop date – start date + 1).
Duration of Asthma	Duration of asthma (months)	The duration of asthma = (first dose date of study drug – date asthma first diagnosed)/30.475, where the day of asthma diagnosed is assumed to be the 1st of the month.
Multiple Assessments for the Same Visit	Vital Signs assessments	• All data will be listed in data listings. • The last non-missing assessment of multiple valid assessments within a pre-dose or post-dose study time window will be used for summaries
Spirometry Assessments	Spirometry assessments	• The last of multiple valid assessments within a post-baseline study time window will be used for summaries and statistical testing, except for AUC parameters, where all post-baseline assessments in the study time window will be used.
Tine to onset of response	Time to onset of response	Time to Onset of Response (minutes) = (time of first achievement of a $\geq$ 15% (or 12%) increase in FEV_1 from baseline, within 30 minutes of dose – treatment administration time).
Time to offset of response	Time to offset of response	Time to Offset of Response: For responders only: (time of first assessment after achievement of response for which the increase from baseline in FEV_1 is < 15% (or 12%) – treatment administration time). If offset of FEV1 < 15% (or 12%) is not achieved and the last available

Category	Description	Data Handling Rules
		assessment is ≥ 15% (or 12%), the time to offset will be defined as (the time of the last available assessment – treatment administration time
Duration of response	Duration of response	Duration of Response = time of offset of Response – time of onset of Response
Special Lab Value Handling	Lab values with a prefix such as: '>', '<', '+' and 'Less than' etc…	• '>': use the available original value +0.001 in the analyses. • '<': use the available original value –0.001 in the analyses. • '+': use the available original value without the prefix in the analyses. • '>=': use the available original value in the analyses. • '<=': use the available original value in the analyses.
Prior, Concomitant, and Post-treatment Medication/ Treatment	Prior, concomitant, and post-treatment medication/treatment	1. Prior medication/treatment is any medication/treatment taken prior to Visit 1, even if this medication continued after Visit 1. A medication/treatment will be considered prior if: a. The start and end date of the medication/treatment are missing, or b. The start date is missing and the end date is on or after Visit 1, or c. Either the medication/treatment start date or end date or both are before Visit 1. 2. Concomitant medication/treatment is any medication/treatment taken on or after Visit 1and on or before the date prior to the last dose of study drug for the subject. A medication/treatment will be identified as concomitant if: a. Medication/treatment start date is after Visit 1 to the date prior to the last dose of study drug, or b. The end date is after Visit 1 to the date prior to the last dose of study drug for the subject, or

Category	Description	Data Handling Rules
		c. 'Ongoing' is checked. 3. A medication with an onset date on or after the last dose of study drug for the subject will not be considered concomitant, but will be considered a **Post-Treatment medication/treatment**. 4. Any medication/treatment which cannot be identified as Prior, Concomitant, or Post-Treatment will be considered as being in each of the categories that are possible from the available information.
Adverse Event	Missing severity	For the AE summary by severity, an AE with missing severity will be deemed as Severe. Imputed values will not be listed in data listings.
	Missing relationship to study drug	For AE summary by relationship, an AE with a missing relationship to study drug (yes/no) will be deemed as Related. Imputed values will not be listed in data listings.
	Treatment-emergent adverse event	An adverse event is considered treatment-emergent if the date of onset is on or after the date of first dose of study drug. The study site will enter a new onset date when there is an increase in severity or intensity for a pre-existing event after the start of a study drug.
		If the AE start date is partial/missing, then • If AE start date is completely missing, then the AE is considered as treatment emergent. • If both AE start month and day are missing and AE start year is the same or after the first dose year, then the AE is considered as treatment emergent. • If AE start day is missing and AE start year and month are the same or after the first dose year and month, then the AE is considered as treatment emergent. Missing/incomplete (partial) AE start and end

Category	Description	Data Handling Rules
		dates will not be imputed for data listings.
Exposure (days)	Exposure (days) (Treatment Duration)	Exposure is defined as the number of days at which doses were administered.
Hard Coding	Hard coding for data analysis	Hard Coding is not allowed during data analysis unless it is agreed to in writing by AstraZeneca.

APPENDIX 2 ANALYSIS DATASET SPECIFICATIONS

Analysis datasets will be built to gain efficiency and ensure consistency in data analyses and presentation for this trial. The specifications for each analysis data set will be prepared separately and will not be a part of this SAP.

APPENDIX 3 SAS CODE FOR STATISTICAL ANALYSES

Test	Template SAS Code for Modeling (SAS Version 9.4)
Linear Mixed Model analysis for a continuous efficacy endpoint, change from baseline in AUC_{0-6}, change from baseline in AUC_{0-4}, or Peak Change from Baseline in FEV_1. Use this code for the analysis of the primary and secondary endpoints.	PROC MIXED PLOTS (ALL) METHOD=REML; CLASS SUBJECT PERIOD TRT SEQUENCE ; MODEL Y = BASE PERIOD TRT SEQUENCE / DDFM=KENWARDROGER SOLUTION VCIRY OUTP=OUT; RANDOM SUBJECT; LSMEANS TRT / PDIFF CL ALPHA=0.05 CORR COV; ODS OUTPUT LSMEANS=MEANS; ODS OUTPUT DIFFS=DIFF; RUN; Where BASE is the baseline value of the endpoint and TRT is the treatment. THE PLOTS (ALL) OPTION FOR PROC MIXED WILL BE USED TO GET PLOTS TO PERFORM MODEL DIAGNOSTICS (for normality and heterogeneity of variance). Scaled residuals will be used. Influence statistics will be requested. If the assumption of homogeneity does not hold (sample variances appear heterogeneous), the following will replace the Random subject and ODS statements above. REPEATED **TRT** / TYPE=UN (or CSH) SUBJECT=SUBJECT; LSMEANS TRT / PDIFF CL ALPHA=0.05 CORR COV; ODS OUTPUT LSMEANS=MEANS; ODS OUTPUT DIFFS=DIFF;
Linear mixed effects model for a continuous efficacy endpoint involving multiple measures per period. Use this	PROC MIXED PLOTS (ALL) METHOD=REML; CLASS SUBJECT PERIOD TRT SEQUENCE ; MODEL Y = BASE PERIOD TRT TIMEPOINT TRT*TIMEPOINT SEQUENCE / DDFM=KENWARDROGER SOLUTION VCIRY OUTP=OUT; RANDOM SUBJECT; REPEATED TIMEPOINT / TYPE=UN SUBJECT=SUBJECT; LSMEANS TRT*TIMEPOINT / PDIFF CL ALPHA=0.05

code for the Other Efficacy parameter Change from Baseline in FEV_1 at each post-dose timepoint at 5, 15, 30, 45, 60, 120, 180, 240, 300, and 360 Minutes Post Dose.	CORR COV; ODS OUTPUT LSMEANS=MEANS; ODS OUTPUT DIFFS=DIFF; RUN; Where BASE is the baseline value of the endpoint and TRT is the treatment. One model includes all time points.
Generalized mixed effects model for an other efficacy categorical endpoint, percentages of subjects achieving a 12% and 15% improvement from baseline within 30 minutes post dose.	PROC GLIMMIX METHOD=QUAD; CLASS TRT(REF=FIRST) PERIOD SUBJECT; MODEL Y=TRT PERIOD / DIST=BIN LINK=LOGIT; RANDOM INT / SUBJECT=SUBJECT; LSMEANS TRT / DIFF OR; RUN; Where TRT is the treatment.
Non-parametric descriptive statistics and CI's of the treatment differences for Time to Peak FEV_1, Time to onset of response, and Duration of response (as appropriate)	The following macro can be used to calculate the point estimate and confidence interval of the Hodges-Lehmann's median for paired data (Han L, Paper ST-154): %macro HL_paired(dsn=, trt1=, trt2=, alpha=); *** STEP 1: Calculate the differences between each pair of treatments for each subject and record the sample size as a macro variable for later use. Note that the macro only calculates differences for 2 treatments so repeat this macro as needed. DATA ONE; SET &DSN; CALL SYMPUT('SIZE',TRIM(LEFT(_N_))); DIFF=&TRT1-&TRT2; RUN;

*** STEP 2: Use ARRAY to form all possible ordered pairs of differences and average values;

```
PROC TRANSPOSE DATA=ONE OUT=TWO(DROP=_NAME_);
VAR DIFF;
RUN;
DATA THREE; SET TWO;
ARRAY X{&SIZE} COL1-COL&SIZE;
DO I=1 TO &SIZE;
DO J= I TO &SIZE;
STAT=(X{I}+X{J})/2;
OUTPUT;
END;
END;
```

*** STEP 3: Calculate the point estimate of the Hodges-Lehmann median difference;

```
PROC SORT DATA=THREE;
BY STAT;
RUN;
PROC MEANS MEDIAN NOPRINT;
VAR STAT;
OUTPUT OUT=EST(DROP=_FREQ_ _TYPE_)
MEDIAN=ESTIMATE;
RUN;
```

*** STEP 4: Calculate the confidence interval of the Hodges-Lehmann median difference;

```
DATA FOUR;
LOWORD=1+INT(&SIZE*(&SIZE+1)/4 + PROBIT(&ALPHA/2)
*SQRT(&SIZE*(&SIZE+1)*(2*&SIZE+1)/24));
UPPORD= CEIL(&SIZE*(&SIZE+1)/4 + PROBIT(1-&ALPHA/2)
*SQRT(&SIZE*(&SIZE+1)*(2*&SIZE+1)/24));
RUN;
DATA FIVE; SET THREE END=LAST;
IF _N_=1 THEN SET FOUR;
RETAIN LOWER UPPER;
IF _N_=LOWORD THEN LOWER=STAT;
IF _N_=UPPORD THEN UPPER=STAT;
IF LAST THEN OUTPUT;
KEEP LOWER UPPER;
RUN;
```

	*** STEP 5: Put the point estimate and confidence into one dataset; DATA HL_EST; MERGE EST FIVE; RUN; %MEND HL_PAIRED;
Linear mixed effects model for duration of response parameters when a parametric analysis is appropriate (Hodges-Lehmann code below when a non-parametric analysis is appropriate)	PROC MIXED PLOTS (ALL) METHOD=REML; CLASS SUBJECT PERIOD TRT SEQUENCE ; MODEL Y = BASE PERIOD TRT SEQUENCE / DDFM=KENWARDROGER SOLUTION VCIRY OUTP=OUT; RANDOM SUBJECT; LSMEANS TRT / PDIFF CL ALPHA=0.05; ODS OUTPUT LSMEANS=MEANS CORR COV; ODS OUTPUT DIFFS=DIFF; RUN; Where BASE is the baseline value of the endpoint and TRT is the treatment.
Descriptive statistics for Percentage of subjects achieving 12% improvement in FEV_1 from baseline within 30 minutes of dose and Percentage of subjects achieving 15% improvement in FEV_1 from baseline within 30 minutes of dose	PROC FREQ; TABLES Y / OUT=FREQCOUNT SPARSE; BY TRT; RUN; Where TRT is the treatment.
Linear Mixed Model analysis for a continuous efficacy endpoint, change	PROC MIXED PLOTS (ALL) METHOD=REML; CLASS SUBJECT PERIOD TRT SEQUENCE ; MODEL Y = BASE PERIOD TRT SEQUENCE SUBGROUP TRT*SUBGROUP / DDFM=KENWARDROGER VCIRY SOLUTION OUTP=OUT;

from baseline in AUC_{0-6}, change from baseline in AUC_{0-4}, or Peak Change from Baseline in FEV_1. Use this code for the subgroup analysis of the primary and secondary endpoints.	RANDOM SUBJECT; LSMEANS TRT|SUBGROUP / PDIFF CL ALPHA=0.05 CORR COV; ODS OUTPUT LSMEANS=MEANS; ODS OUTPUT DIFFS=DIFF; RUN; Where BASE is the baseline value of the endpoint, TRT is the treatment, and SUBGROUP is 1=ICS Use at Screening and 2=No ICS Use at Screening THE PLOTS (ALL) OPTION FOR PROC MIXED WILL BE USED TO GET PLOTS TO PERFORM MODEL DIAGNOSTICS (for normality and heterogeneity of variance). Scaled residuals will be used.

APPENDIX 4 MOCKUP TABLES, LISTINGS, AND GRAPHS (TLGS)

Mockup tables, listings, and graphs are presented in a separate document.

APPENDIX 4 SPECIFICATION OF END-OF-TEXT STANDARD OUTPUT TABLES, LISTINGS, AND FIGURES (TLFs)

Protocol Title: A Randomized, Double-blind, Single dose, Placebo-controlled, 5-Period, 5-Treatment, Crossover, Multi-center, Dose-ranging Study to Compare PT007 to Placebo MDI and Open-Label Proventil® HFA in Adult and Adolescent Subjects With Mild to Moderate Asthma

PT007001

Trial Sponsor:	AstraZeneca AB
Study Number:	D6930C00001 (PT007001)
Study Phase:	II
Product Name:	Albuterol Sulfate Pressurized Inhalation Suspension (AS MDI); PT007
PIND Number:	136213
Indication:	Asthma
Dosage Form/Strength	• AS MDI as o 2 actuations of 45 µg per actuation (90 µg) o 2 actuations of 90 µg per actuation (180 µg)

Date of Issue: 13 Mar 2018
Version 1.0

General Instructions for End-of-Text TFLs

Following are the specifications for end of text standard Tables, listings, and Figures (TFLs).

Header

The following header should appear at the very top of each page of a Table, a listing, or a Figure (TLF):
Protocol PT007001 Albuterol Sulfate Pressurized Inhalation Suspension

Footer

The following footer should appear at the bottom of each page of a TLF generated in SAS:

Report generated by program:/sasdir/PGNAME.sas Version YYYY-mm-dd hh:mm (Page n of N)

where: PGNAME = SAS program name. Version will be replaced by "Draft" or "Final". Page number will be right-justified.

Title

At least two (2) lines should be reserved for the whole title. The first line of the title is for the TLF number (i.e., title index #) and the actual title (title); a longer title may continue onto subsequent lines. The analysis analysis set descriptor (Analysis Set) will be specified on the line following the title line(s). All titles should be centered, as shown in the following example:

Table 1.5.3 Demographics
Analysis Set: Safety Analysis Set

Footnotes

- In general, a footnote serves as a brief explanation/clarification/definition/concept of a flag symbol or a character, an abbreviation, a terminology, etc., that appears in or related directly to the displayed content of a TLF. Detailed/technical elaboration of, for example, a mathematical/statistical formula, a statistical term/test, or an algorithm for deriving a parameter value, should be addressed in the text of the statistical analysis plan (SAP).
- All footnotes should follow immediately after a horizontal solid line. There should be one and only one space between the last footnote and the footer.
- Each line of a complete footnote should end with a period. When a footnote needs more than 1 line, one (1) period is needed.
- Large data listings will have footnotes on the first page only.

Row Labels/Column Labels: The mockups will reflect the preferred style of capitalization.

Page Layout

- All output should be in landscape orientation. A margin of 1.5, 1, 1, and 1 inch should be on the top, right, left, and bottom, respectively.
- All efforts should be made to present all Treatment groups in one page.
- When 3 or more Treatment groups are designed for a study and if it is not possible to fit all of them in one page, the 4th and 5th treatment groups should be displayed on the 2nd page, etc. The Study Biostatistician will pre-determine the order for the display of the treatment groups.

Page Format

- There should be a solid line at the top of the Tables and listings just below the title.
- There should be a solid line just below the column headings that runs completely across the width of the Tables and listings.
- There should be a solid line at the bottom of the Tables and listings just above the footnote(s) on every page.

Font

- The default font to be used in the actual study Tables/listings should be Courier New 8 point which is approximately equivalent to the accepTable font size of Times New Roman 9-10 in accordance with the FDA's guidance on Electronic Common Technical Document Specification.
- The use of Courier New 7 point is optional for some Tables/listings and will be determined at the study level by the Study Biostatistician and Study Programmer. However, it is recommended that this option be used primarily for data listings.

Descriptive Statistics

By default, descriptive statistics in this template covers: n, Mean, Median, Standard Deviation (SD), Minimum (Min), and Maximum (Max). Unless otherwise specified in the actual Table shells, the mean, standard deviation, standard error of the mean, and median should be displayed to one more decimal place than the original data. The standard error of the mean will be displayed with at least 2 significant digits for efficacy Tables.

Rounding for Percentage

Unless specified in the actual Table shells for a study, all percentages will be rounded to 1 decimal place in all TLFs. Percentage signs will not be included in the body of the Table (i.e., 99.9 will be displayed, not 99.9%), but may be included in row or column headings.

Unless specified in the actual Table shells for a study, p-values will be presented with 4 decimal places.

Alignment of Decimals

- It is recommended that all the decimal places be aligned in summary Tables, as shown in the following example:

	Decimal Align
n	xxx
Mean	xx.xx
SD	xx.xx
Median	xx.xx
Minimum, Maximum	xx.x, xx.x

- When numbers with decimal points are included in brackets (e.g., percentages), have the brackets aligned to the right and then padded to allow for all possible percentages and then the left brackets will also be aligned. For example:

Brackets Align	
(99.9)	(xx.x)
(9.9)	(x.x)

- It is recommended that all column entries in a summary Tables and listings are aligned to the center.
- Columns for text fields are all left justified. Columns with whole numbers are all right justified.
- For graphs, the lines are distinguishable and that the symbols for each line are appropriate. Legend is consistent across output for Treatment names and abbreviations.

Use of N Versus n

- N = total number of subjects in the defined analysis set.
- n = total number of subjects in the specific category.
- If N is specified in the column heading then any reference to the number of subjects in the body should be small n, as shown in the following example:

Demographic Parameter	Treatment Group A (N=XXX)	Treatment Group B (N=XXX)	Total (N=XXX)
Age (years)			
n	xxx	xxx	xxx
Mean	xx.x	xx.x	xx.x
SD	x.x	x.x	x.x
Median	xx.x	xx.x	xx.x
Minimum, Maximum	xx, xx	xx, xx	xx, xx

A Note for Subject Data Listings

- Observed Dates/AE Severity/Relationship to investigational product are used in subject data listings.
- Observed values or raw assessment scores are used in data listings along with their derived values used in analyses, e.g., raw assessment scores and derived total scores.

Table of Contents

1. Subject Disposition, Demographic, Baseline, and Other Summary Tables

Table 1.1.1 Subject Disposition
Analysis Set: All Screened Subjects

	All Subjects (N=xxx)
	n (%)
Not Treated	xx (xx.x)
Treated	xx (xx.x)
Treated with AS MDI 90 µg	xx (xx.x)
Treated with AS MDI 180 µg	xx (xx.x)
Treated with Proventil 90 µg	xx (xx.x)
Treated with Proventil 180 µg	xx (xx.x)
Treated with Placebo	xx (xx.x)
Length of Subject Participation in the Study	
5 Treatment Periods	xx (xx.x)
4 Treatment Periods	xx (xx.x)
3 Treatment Periods	xx (xx.x)
2 Treatment Periods	xx (xx.x)
1 Treatment Period only	xx (xx.x)
0 Treatment Periods	xx (xx.x)
Completed Study	xx (xx.x)
Premature Discontinuation	xx (xx.x)
ITT Analysis Set [a]	xx (xx.x)
mITT Analysis Set [b]	xx (xx.x)
Safety Analysis Set [c]	xx (xx.x)
Not Randomized Analysis Set [d]	xx (xx.x)

[a] The Intent-To-Treat (ITT) Analysis Set was defined as all subjects who were randomized to treatment and received at least 1 dose of the study treatment. Subjects were analyzed in each period according to the treatment they were assigned to per the randomization scheme (Note that a subject who used a study treatment but took less than 1 full dose of treatment qualified for this analysis set).
[b] The mITT Analysis Set was defined as a subset of the ITT analysis set including subjects who received treatment and had post-treatment efficacy data from at least 2 Treatment Periods. Data judged to be impacted by major protocol deviations was determined prior to unblinding and excluded per the statistical protocol deviation plan. Statistical tabulations and analyses were by randomized treatment, but data obtained after subjects received an incorrect treatment were excluded from the affected periods.
[c] The Safety Analysis Set was defined as all subjects who were randomized to treatment and received at least 1 dose of the study treatment. Subjects were analyzed according to treatment received rather than per the randomization scheme.
[d] The Not Randomized analysis set was defined as subjects who did not receive a randomization number and therefore did not receive a dose of study treatment (eg, subjects who were screen failures or stopped participation before being randomized).

Table 1.1.2 Reasons for Subjects Not Randomized
Analysis Set: All Subjects Not Randomized

	All Subjects Not Randomized (N=xxx)
Reason Not Randomized	n (%)
Any Inclusion/Exclusion Criterion	xxx (xx.x)
Exclusion Criterion #x: xxxx xxxx xx xxxxx xxxxx xxxx	xxx (xx.x)
Exclusion Criterion #x: xxx xxxxxxxxxxx xx xxxxx x	xxx (xx.x)
Inclusion Criterion #x: xx x x xxx xxxx xxxx xxxxxxxxxxx	xxx (xx.x)
Inclusion Criterion #x: xxxx xxxx xx xxxxx xxxxx xxxx	xxx (xx.x)
FAny Failure of Randoimzation Criteria	xxx (xx.x)
Cfiteria #X; XXXXXXXXXXXXXXXXXXXXXXX	xxx (xx.x)

Note: Reasons of Other are listed by subject in Listing 1.X.

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Notes to Programmer: Order by frequency within each category. Display all protocol-specified criteria shown on the End of Treatment/ CRF that have counts> 0..
From Section 3.3.1 of the Protocol, the Randomization Criteria are:
1. Subjects of childbearing potential must have a negative urine pregnancy test
2. Received no asthma medication other than Sponsor-provided Pulmicort Flexhaler 180 µg or 360 µg BID as assigned and/or Sponsor-provided Ventolin from Visit 1 to Visit 2, except for allowable allergy medications defined in Table 8 *of the Protocol.*
3. The last dose of Pulmicort Flexhaler (if applicable) was the previous night (ie, morning dose of Pulmicort Flexhaler was not administered), and the last dose of Sponsor-provided Ventolin was no later than 6 hours before the study visit (if Ventolin is needed in the morning, the visit must be rescheduled)
4. Pre-bronchodilator FEV1 ≥40% percent predicted normal value
5. Has not used >8 actuations per day (ie, 4 doses of 2 actuations per day) of Sponsorprovided Ventolin for rescue on more than any 3 days during the previous 7 days
6. No upper respiratory infection, lower respiratory infection, or asthma exacerbation during the Screening Period
7. Demonstrate acceptable MDI administration technique
8. Able to comply with all study procedures

Table 1.1.3 Exclusions From ITT, mITT, and Safety Analysis Sets
Analysis Set: All Subjects Randomized

Subject ID	Treatment Sequence	Analysis Set Excluded	Period Excluded	Timepoints Excluded	Variable(s) Excluded	Reason for Exclusion
Study Center # / (Investigator): ### / (xxxxxxxxxx)						
xxxxx	-/-/-/-/-	ITT	All	All	All	Subject did not receive treatment in at least 1 treatment period.
		mITT	All	All	All	Subject did not have post-treatment efficacy data from at least 2 Treatment Periods.
		Safety	All	All	All	Did not receive at least one dose of the study treatment in the study.
		mITT	Period 1	300, 360 Minutes	All	Subject did not have post-treatment efficacy data from at least 2 Treatment Periods.
xxxxx	A/B/E/C/D	Safety	All	All	All	Subject did not receive treatment in at least 1 treatment period.
xxxxx	B/C/-/-/-	ITT	All	All	All	Subject did not receive treatment in at least 1 treatment period.
		mITT	All	All	All	Subject did not have post-treatment efficacy data from at least 2 Treatment Periods.
		Safety	All	All	All	Did not receive at least one dose of the study treatment in the study.
xxxxx	A/E/-/-/-	mITT	All	All	All	Subject took incorrect study medication.
xxxxx	B/A/C/E/-	mITT	Period 4	All	All	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx.

Treatment: A = Placebo, B = AS MDI 90 µg, C = AS MDI 180 µg, D = Proventil 90 µg, E = Proventil 180 µg, - = Not Treated.
Subjects may be included in a analysis set as a whole, but have period or timepoint data excluded.

Report generated by program: PT007001/sasdir/programs/statout/t010103.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer:

Sort by Study Center, Investigator, and Subject within Study Center.

List records per subject, analysis set excluded, period excluded, and timepoint excluded.

Move 'Study Center/Inv' row header to the next page whenever there is not enough room on current page to fit at least one row of data underneath this header.

Table 1.2.1 Reason for Premature Treatment Discontinuation
Analysis Set: ITT Analysis Set

	Placebo (N=xxx)	AS MDI 90 µg (N=xxx)	AS MDI 180 µg (N=xxx)	Proventil 90 µg (N=xxx)	Proventil 180 µg (N=xxx)
	n (%)	n (%)	n (%)	n (%)	n (%)
Premature Treatment Discontinuation	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Reason for Premature Treatment Discontinuation					
Administrative Reasons	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Adverse Event	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Lack of Efficacy	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subject Discretion	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Withdrawal of Consent					
Asthma	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Investigator or Designee Considers it to be in the Best Interest of the Subject	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subject Lost-to-Follow-up	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Major Protocol Deviation	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Protocol-Specified Discontinuation Criteria	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
FEV_1 Stability Criteria Sec 5.1.4	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Requirement of any Prohibited Medications Listed in Sec 7.7.3	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Positive Pregnancy Test	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Asthma Worsening Requiring Change in Asthma Treatment Sec 3.9	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
The Subject's Treatment Code Prematurely Broken by Investigator	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Note: Reasons of Other are listed by subject in Listing 1.2.

Report generated by program: PT007001/sasdir/programs/statout/t010201.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer:Sort by descending frequency of major reason category using AS MDI column. Within a major reason category, sort by descending frequency of subcategory using AS MDI column.

Table 1.2.2 Reason for Premature Treatment Discontinuation
Analysis Set: mITT Analysis Set

Footnotes:
Subjects were included in summaries for a treatment if they received at least one dose of the treatment.

Table 1.2.3 Reason for Premature Treatment Discontinuation
Analysis Set: Safety Analysis Set

Footnotes:
Subjects were included in summaries for a treatment if they received at least one dose of the treatment.

Table 1.3 Analysis Sets by Treatment
Analysis Set: All Subjects Randomized

	Placebo (N=xxx)	AS MDI 90 µg (N=xxx)	AS MDI 180 µg (N=xxx)	Proventil 90 µg (N=xxx)	Proventil 180 µg (N=xxx)
	n (%)	n (%)	n (%)	n (%)	n (%)
Intent-to-treat Analysis Set [a]	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
mITT Analysis Set [b]	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Safety Analysis Set [c]	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

n = number of subjects in the category, N=# of subjects who were randomized to the treatment, % = 100 x n/N.
[a] The Intent-To-Treat (ITT) Analysis Set was defined as all subjects who were randomized to treatment and received at least 1 dose of the study treatment. Subjects were analyzed in each period according to the treatment they were assigned to per the randomization scheme (Note that a subject who used a study treatment but took less than 1 full dose of treatment qualified for this analysis set).
[b] The mITT Analysis Set was defined as a subset of the ITT analysis set including subjects who received treatment and had post-treatment efficacy data from at least 2 Treatment Periods. Data judged to be impacted by major protocol deviations were determined prior to unblinding and excluded per the statistical protocol deviation plan. Statistical tabulations and analyses were by randomized treatment, but data obtained after subjects received an incorrect treatment was excluded from the affected periods.
[c] The Safety Analysis Set was defined as all subjects who were randomized to treatment and received at least 1 dose of the study treatment. Subjects were analyzed according to treatment received rather than per the randomization scheme.

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Table 1.4 Reason for Exclusion From the mITT Analysis Set
Analysis Set: ITT Analysis Set

Reason for	Placebo (N=xxx) n (%)	AS MDI 90 µg (N=xxx) n (%)	AS MDI 180 µg (N=xxx) n (%)	Proventil 90 µg (N=xxx) n (%)	Proventil 180 µg (N=xxx) n (%)
Exclusion of a Subject from mITT Analysis Set	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
<Reason 1>	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
<Reason 2>	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
…					
Exclusion of a Treatment Period from mITT Analysis Set	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
<Reason 1>	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
<Reason 2>	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
…					

Subjects may have multiple reasons for exclusion; therefore, counts for individual reasons may not add up to the total number of subjects excluded from the analysis set.

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Note to the Programmer: Subjects are to be included in summaries and N= in the column header for a treatment if they attended a visit designated for a treatment in their treatment sequence.

Table 1.5.1 Demographics and Baseline Characteristics
Analysis Set: mITT Analysis Set

Parameter	All Subjects (N=xxx)
Age (Years)[a]	
n	xxx
Mean	xx.x
SD	xx.x
Median	xx.x
Minimum	xx
Maximum	xx
Age Group, n (%)	
Age 12 to < 18 years	xxx (xx.x)
Age 18 to 65 years	xxx (xx.x)
Missing	x (xx.x)
Gender, n (%)	
Male	xxx (xx.x)
Female	xxx (xx.x)
Missing	x (xx.x)
Race, n (%)	
Black or African American	xx (xx.x)
White	xxx (xx.x)
Native Hawaiian or Other Pacific Islander	xx (xx.x)
American Indian or Alaska Native	xx (xx.x)
Asian	xx (xx.x)
Other	xx (xx.x)
Missing	xx (xx.x)
Ethnicity, n (%)	
Hispanic	xxx (xx.x)
Not Hispanic or Latino	xxx (xx.x)
Unknown	xxx (xx.x)
Not Reported	xx (xx.x)
Smoking Status, n (%) [b]	
Former Smoker	xxx (xx.x)
Non Smoker	xxx (xx.x)
Missing	xxx (xx.x)
Number of Years Smoked	

Parameter	All Subjects (N=xxx)
n	xxx
Mean	xx.x
SD	xx.x
Median	xx.x
Minimum	xx.x
Maximum	xx.x
Average Number of Cigarettes Smoked Per Day	
n	xxx
Mean	xx.x
SD	xx.x
Median	xx.x
Minimum	xx.x
Maximum	xx.x
Number of Pack Years Smoked [c]	
n	xxx
Mean	xx.x
SD	xx.x
Median	xx.x
Minimum	xx.x
Maximum	xx.x
Prior Asthma Medication	
SABA prn only, n (%)	xx.x
ICS, n (%)	xx.x
ICS/LABA, n (%)	xx.x
Weight (kg)	
n	xxx
Mean	xx.x
SD	xx.x
Median	xx.x
Minimum	xx.x
Maximum	xx.x
Height (cm)	
n	xxx
Mean	xxx.x
SD	xxx.x
Median	xxx.x
Minimum	xxx.x
Maximum	xxx.x
BMI (kg/m^2)	
n	xxx

Parameter	All Subjects (N=xxx)
Mean	xx.x
SD	xx.x
Median	xx.x
Minimum	xx.x
Maximum	xx.x

[a] Age is age at Visit 1. The remaining characteristics were based on data from Screening visits prior to the start of the study.
[b] Former Smoker was defined as those who have stopped smoking for at least 6 months prior to first Screening Visit and have no more than 10 pack years history of smoking.
[c] Number of pack years smoked = (number of cigarettes per day / 20) x number of years smoked.

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Notes to Programmer:
Repeat titles, column headers, and footnotes on each page. Keep the summary for a parameter in the same page when breaking the Table into multiple pages.
Sort race by decreasing frequecing. The race/ethnicities of Native Hawaiian or Other Pacific Islander OR American Indian or Alaska Native can be removed from this Table if they do not exist in the database.
Calculate BMI using Height at Visit 1. BMI = weight (kg)/height (m)^2.
Please delete Missing row when there are no missing values.

Table 1.5.2 Demographics and Baseline Characteristics
Analysis Set: ITT Analysis Set

Table 1.5.3 Demographics and Baseline Characteristics
Analysis Set: Safety Analysis Set

Note to Programmer: Remove Table 1.5.3 if Safety Analysis Set is the same as the ITT Analysis Set.

Table 1.5.4 Demographics and Baseline Characteristics
Analysis Set: All Subjects Not Randomized

Table 1.6.1 Duration of Asthma
Analysis Set: mITT Analysis Set

	All Subjects (N=xxx)
Duration of Asthma (months) [a]	
n	xxx
Mean	xx.x
SD	xx.x
25th Percentile	xx.x
Median	xx.x
75th Percentile	xx.x
Minimum	xx.x
Maximum	xx.x

[a] The duration of asthma is calculated relative to the first dose of study medication.

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Notes to Programmer: Duration of Asthma = (First Dose date of Study Treatment - Date Asthma First Diagnosed)/30.4375, where day of Asthma diagnosed is assumed to be the 1st of the month.

Table 1.6.2 Duration of Asthma
Analysis Set: Safety Analysis Set

Table 1.7.1 Screening Pre- and Post-Bronchodilator and Baseline Spirometry Parameters
Analysis Set: mITT Analysis Set

	All Subjects (N=xxx)
FEV_1 (% predicted)	
Visit 1 [a]	
Pre-Ventolin HFA:	
n	xx
Mean	xx.xxx
SD	xx.xxx
25th Percentile	xx.xxx
Median	xx.xxx
75th Percentile	xx.xxx
Minimum	xx.xxx
Maximum	xx.xxx
Post-Ventolin HFA:	
n	xx
Mean	xx.xxx
SD	xx.xxx
25th Percentile	xx.xxx
Median	xx.xxx
75th Percentile	xx.xxx
Minimum	xx.xxx
Maximum	xx.xxx
Visit 2 (Pre-dose)	
Pre-Ventolin HFA:	
n	xx
Mean	xx.xxx
SD	xx.xxx
25th Percentile	xx.xxx
Median	xx.xxx
75th Percentile	xx.xxx
Minimum	xx.xxx
Maximum	xx.xxx
Post-Ventolin HFA:	
n	xx
Mean	xx.xxx
SD	xx.xxx
25th Percentile	xx.xxx
Median	xx.xxx

75th Percentile	xx.xxx
Minimum	xx.xxx
Maximum	xx.xxx

Repeat the above for these parameters:

FEV_1 (L)
FVC (% predicted)
FVC (L)
FEF 25-75 (% predicted)
FEF 25-75 (L/sec)

[a] Visit 1, for this purpose, was Visit 1, 1a, or 1b, whichever visit had the highest FEV_1 result post-dose.

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Table 1.7.2 Screening Pre- and Post-Bronchodilator and Baseline Spirometry Parameters
Analysis Set: ITT Analysis Set

Table 1.8.1 Reversibility to Ventolin HFA at Screening
Analysis Set: mITT Analysis Set

	All Subjects (N=xxx)
Post-Ventolin HFA FEV_1 - Pre-Ventolin HFA FEV_1 (mL)	
n	xx
Mean	xx.x
SD	xx.x
Median	xx.x
Minimum	xx.x
Maximum	xx.x
Reversibility (%) Post-Ventolin HFA for FEV_1 [a]	
n	xx
Mean	xx.x
SD	xx.x
Median	xx.x
Minimum	xx.x
Maximum	xx.x
Reversible [b], n (%)	xx (xx.x)

If a subject was missing a Post- or Pre-Ventolin HFA FEV_1 value at Screening Visit 1, these values were replaced by the Pre- and Post-Ventolin HFA values from Screening Visit 1a. Similarly, if values were missing at Screening Visits 1 and 1a, the values were replaced by those from Screening Visit 1b.
[a] Reversibility (%) is defined as 100 x (the change from pre-Ventolin HFA to post for FEV_1)/pre-Ventolin HFA FEV_1.
[b] Reversible is defined as Improvement in FEV_1 post-Ventolin HFA administration compared to pre-Ventolin HFA of >=15%.

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Table 1.8.2 Reversibility to Ventolin HFA at Screening
Analysis Set: ITT Analysis Set

Table 1.9 Medical/Surgical History
Analysis Set: Safety Analysis Set

	All Subjects (N=xxx)
	n (%)
Subject Had Medical/Surgical History	
No	xxx (xx.x)
Yes	xxx (xx.x)
Cardiovascular	xxx (xx.x)
CNS/Neurological	xxx (xx.x)
Dermatologic	xxx (xx.x)
Drug Allergy	xxx (xx.x)
EENT	xxx (xx.x)
Endocrine/Metabolic	xxx (xx.x)
Gastrointestinal	xxx (xx.x)
Genitourinary	xxx (xx.x)
Hepatic	xxx (xx.x)
Hematologic	xxx (xx.x)
Immunological	xxx (xx.x)
Malignancy	xxx (xx.x)
Musculoskeletal	xxx (xx.x)
Psychiatric	xxx (xx.x)
Respiratory	xxx (xx.x)
Renal	xxx (xx.x)
Other	xxx (xx.x)

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Note to Programmer: Please sort by descending frequency of occurrence in All Subjects. Denominator should be N from the column header for a treatment.

Table 1.10.1 Prior Medications – Asthma-Related
Analysis Set: Safety Analysis Set

Preferred Term	All Subjects (N=xxx) n (%)
Any Prior Asthma Medication	xxx (xx.x)
Medication 1	xxx (xx.x)
Medication 2	xxx (xx.x)

Preferred term is according to WHODRUG Qxxxx.

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Notes to Programmer: Sort Medications by descending frequency of use in All Subjects.

Table 1.10.2 Prior Medications-Other than Asthma-Related
Analysis Set: Safety Analysis Set

Notes to Programmer: Sort Medications by descending frequency of use for All Subjects. Add a row for "Any Prior Other Medication".

Table 1.11.1a Concomitant Medications During Treatment Period – Asthma-Related
Analysis Set: Safety Analysis Set

Preferred Term	Placebo (N=xxx) n (%)	AS MDI 90 µg (N=xxx) n (%)	AS MDI 180 µg (N=xxx) n (%)	Proventil 90 µg (N=xxx) n (%)	Proventil 180 µg (N=xxx) n (%)
Any Concomitant Asthma Medication	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Medication 1	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Medication 2	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)

Preferred term is according to WHODRUG Qxxxx.
All subjects were allowed only sponsor-provided Ventolin HFA and/or Pulmicort Flexhaler for relief of symptoms.
See Listing 6.4 for the use of Ventolin HFA as rescue medication.

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Notes to Programmer: Sort Medications by descending frequency of use in All Subjects.

Table 1.11.1b Concomitant Medications During Washout Period – Asthma-Related
Analysis Set: Safety Analysis Set

Concomitant medications are tabulated by the treatment received during the Treatment Period just prior to the washout.
Preferred term is according to WHODRUG Qxxxx.
All subjects were allowed only sponsor-provided Ventolin HFA and/or Pulmicort Flexhaler for relief of symptoms.
See Listing 6.4 for the use of Ventolin HFA as rescue medication.

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Table 1.11.2.a Concomitant MedicationsDuring Treatment Period-Non-Asthma Related
Analysis Set: Safety Analysis Set

Notes to Programmer: Sort Medications by descending frequency of use in All Subjects. Add a row for "Any Concomitant Other Medication".

Table 1.11.2b Concomitant Medications During Washout Period-Non-Asthma Related
Analysis Set: Safety Analysis Set

Notes to Programmer: Sort Medications by descending frequency of use in All Subjects. Add a row for "Any Concomitant Other Medication

2. Efficacy Summary Tables and Figures

Primary Efficacy Endpoint

Table 2.1.1 Change from Baseline in FEV_1 AUC_{0-6} (L) Overall and by ICS Use Subgroups
Analysis Set: mITT Analysis Set

Treatment	Baseline FEV_1	Change From Baseline AUC_{0-6}	LS Mean Differences Between Treatments			
			Placebo	AS MDI 90 µg	Proventil 180 µg	Proventil 90 µg
Combined ICS Use Groups [a]						
AS MDI 180 µg						
N	xx	xx				
Mean	x.xxx	x.xxx				
SD	x.xxx	x.xxx				
Median	x.xxx	x.xxx				
Min-Max	x.xxx-x.xxx	x.xxx-x.xxx				
LS Mean (SE)		x.xxx (x.xxxx)	x.xxx (x.xxxx)	x.xxx (x.xxxx)	x.xxx (x.xxxx)	x.xxx (x.xxxx)
95% CI		(x.xxx, x.xxx)	(x.xxx, x.xxx)	(x.xxx, x.xxx)	(x.xxx, x.xxx)	(x.xxx, x.xxx)
P-value			x.xxxx	x.xxxx	x.xxxx	
AS MDI 90 µg						
N	xx	xx				
Mean	x.xxx	x.xxx				
SD	x.xxx	x.xxx				
Median	x.xxx	x.xxx				
Min-Max	x.xxx-x.xxx	x.xxx-x.xxx				
LS Mean (SE)		x.xxx (x.xxxx)	x.xxx (x.xxxx)	Not Applicable	x.xxx (x.xxxx)	x.xxx (x.xxxx)
95% CI		(x.xxx, x.xxx)	(x.xxx, x.xxx)		(x.xxx, x.xxx)	(x.xxx, x.xxx)
P-value			x.xxxx			x.xxxx
Proventil 180 µg						
N	xx	xx				
Mean	x.xxx	x.xxx				
SD	x.xxx	x.xxx				
Median	x.xxx	x.xxx				
Min-Max	x.xxx-x.xxx	x.xxx-x.xxx				
LS Mean (SE)		x.xxx (x.xxxx)	x.xxx (x.xxxx)	Shown Above	Not Applicable	x.xxx (x.xxxx)
95% CI		(x.xxx, x.xxx)	(x.xxx, x.xxx)			(x.xxx, x.xxx)
P-value			x.xxxx			x.xxxx
Proventil 90 µg						
N	xx					

Treatment	Baseline FEV_1	Change From Baseline AUC_{0-6}	LS Mean Differences Between Treatments: Placebo	AS MDI 90 µg	Proventil 180 µg	Proventil 90 µg
Mean	x.xxx					
SD	x.xxx					
Median	x.xxx					
Min-Max	x.xxx-x.xxx					
LS Mean (SE)		x.xxx (x.xxxx)	x.xxx (x.xxxx)	Shown Above	Shown Above	Not Applicable
95% CI		(x.xxx, x.xxx)	(x.xxx, x.xxx)			
P-value			x.xxxx			
Placebo						
N	xx					
Mean	x.xxx					
SD	x.xxx					
Median	x.xxx					
Min-Max	x.xxx-x.xxx					
LS Mean (SE)		x.xxx (x.xxxx)	Not Applicable	Shown Above	Shown Above	Shown Above
95% CI		(x.xxx, x.xxx)				

Repeat Above for:
Subgroup: ICS Use at Screening [b]

Repeat Above for:
Subgroup: Did Not Use ICS at Screening [b]

Treatment-by-Subgroup Interaction P-value: 0.xxxx

Baseline is defined as the mean of evaluable 60 and 30 minute pre-dose values across Visits 2, 3, 4, 5, and 6.
ICS = Inhaled Corticosteroid
LS Mean = least squares mean from the the linear mixed effects model
[a] Combined ICS Use Groups Model:
A linear mixed effect model with a random subject effect for the correlation across periods and fixed effects for treatment, treatment sequence, baseline FEV_1, and period.
[b] ICS Use Subgroups Model:
A linear mixed effect model with a random subject effect and fixed effects for treatment, treatment sequence, baseline FEV_1, period, ICS Use subgroup, and treatment-by-subgroup interaction.
The p-value is for the superiority comparison of AS MDI or Proventil to Placebo. The non-inferiority of AS MDI 180 µg to Proventil 180 µg or of AS MDI 90 µg to Proventil 90 µg is concluded when the lower CI limit for the difference between treatments is >-100 mL.

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Note to Programmer: The baseline summary statistics are based on subjects who had at least one data point post-baseline on Day 1.

Table 2.1.2 Change from Baseline in FEV_1 AUC_{0-6} (L) Overall and by ICS Use Subgroups
Analysis Set: ITT Analysis Set

Secondary Efficacy Endpoints

Table 2.2.1 Change from Baseline in FEV_1 AUC_{0-4} (L)
Analysis Set: mITT Analysis Set

Notes to Programmer:
Follow the format of Table 2.1.1.

Table 2.2.2 Peak Change from Baseline in FEV_1 (L)
Analysis Set: mITT Analysis Set

Notes to Programmer:
Follow the format of Table 2.1.1.

Other Efficacy Endpoints

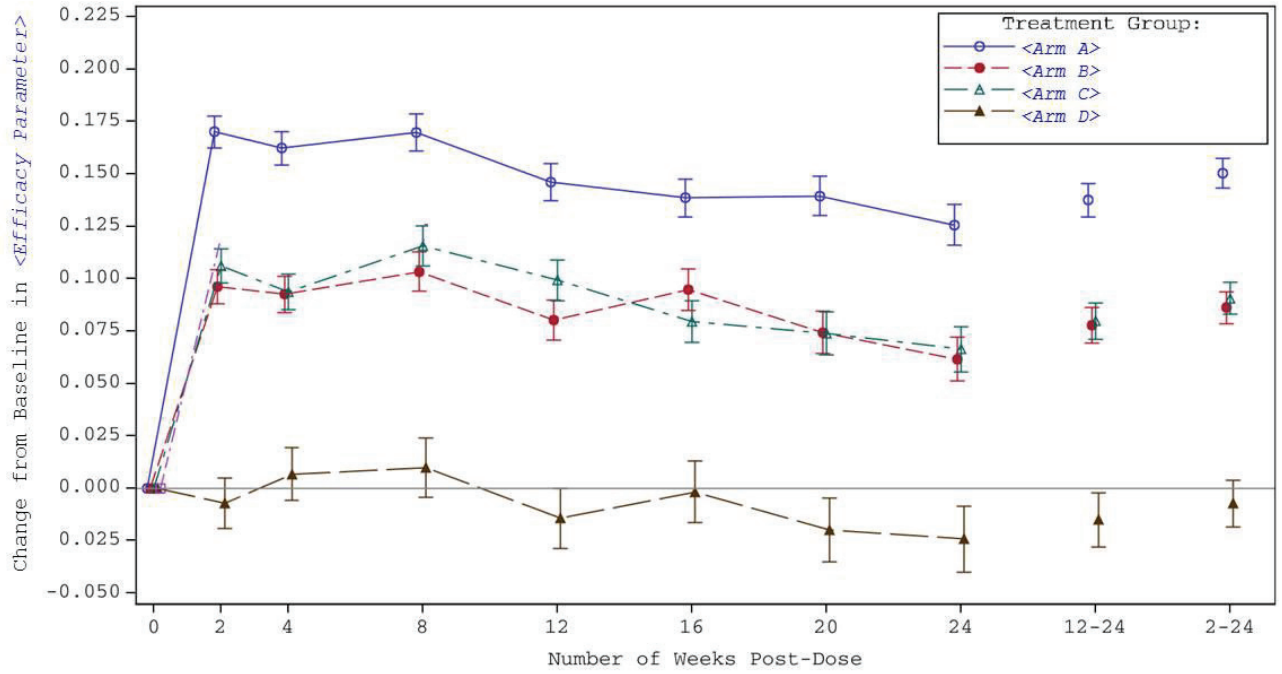
Table 2.3.1 Change from Baseline in FEV_1 (L) by Timepoint
Analysis Set: mITT Analysis Set

Treatment	Baseline FEV_1	Change From Baseline	LS Mean Differences Between Treatments			
			Placebo	AS MDI 90 µg	Proventil 180 µg	Proventil 90 µg
5 Minutes Post-Dose [a]						
AS MDI 180 µg						
N	xx	xx				
Mean	x.xxx	x.xxx				
SD	x.xxx	x.xxx				
Median	x.xxx	x.xxx				
Min-Max	x.xxx-x.xxx	x.xxx-x.xxx				
LS Mean (SE)		x.xxx (x.xxxx)	x.xxx (x.xxxx)	x.xxx (x.xxxx)	x.xxx (x.xxxx)	x.xxx (x.xxxx)
95% CI		(x.xxx, x.xxx)	(x.xxx, x.xxx)	(x.xxx, x.xxx)	(x.xxx, x.xxx)	(x.xxx, x.xxx)
P-value			x.xxxx	x.xxxx	x.xxxx	
AS MDI 90 µg						
N	xx	xx				
Mean	x.xxx	x.xxx				
SD	x.xxx	x.xxx				
Median	x.xxx	x.xxx				
Min-Max	x.xxx-x.xxx	x.xxx-x.xxx				
LS Mean (SE)		x.xxx (x.xxxx)	x.xxx (x.xxxx)	Not Applicable	x.xxx (x.xxxx)	x.xxx (x.xxxx)
95% CI		(x.xxx, x.xxx)	(x.xxx, x.xxx)		(x.xxx, x.xxx)	(x.xxx, x.xxx)
P-value			x.xxxx			x.xxxx
Proventil 180 µg						
N	xx	xx				
Mean	x.xxx	x.xxx				
SD	x.xxx	x.xxx				
Median	x.xxx	x.xxx				
Min-Max	x.xxx-x.xxx	x.xxx-x.xxx				
LS Mean (SE)		x.xxx (x.xxxx)	x.xxx (x.xxxx)	Shwon Above	Not Applicable	x.xxx (x.xxxx)
95% CI		(x.xxx, x.xxx)	(x.xxx, x.xxx)			(x.xxx, x.xxx)
P-value			x.xxxx			x.xxxx

Treatment	Baseline FEV_1	Change From Baseline	LS Mean Differences Between Treatments			
			Placebo	AS MDI 90 µg	Proventil 180 µg	Proventil 90 µg
Proventil 90 µg						
N	xx					
Mean	x.xxx					
SD	x.xxx					
Median	x.xxx					
Min-Max	x.xxx-x.xxx					
LS Mean (SE)		x.xxx (x.xxxx)	x.xxx (x.xxxx)	Shown Above	Shown Above	Not Applicable
95% CI		(x.xxx, x.xxx)	(x.xxx, x.xxx)			
P-value			x.xxxx			
Placebo						
N	xx					
Mean	x.xxx					
SD	x.xxx					
Median	x.xxx					
Min-Max	x.xxx-x.xxx					
LS Mean (SE)		x.xxx (x.xxxx)	Not Applicable	Shown Above	Shown Above	Shown Above
95% CI		(x.xxx, x.xxx)				

Repeat for 30, 45, 60, 120, 180, 240, 300, and 360 minutes.

Figure 2.3.1.1 Change from Baseline in FEV_1 (L) ± SE Over Time
Analysis Set: mITT Analysis Set



Source: Table 2.3.1

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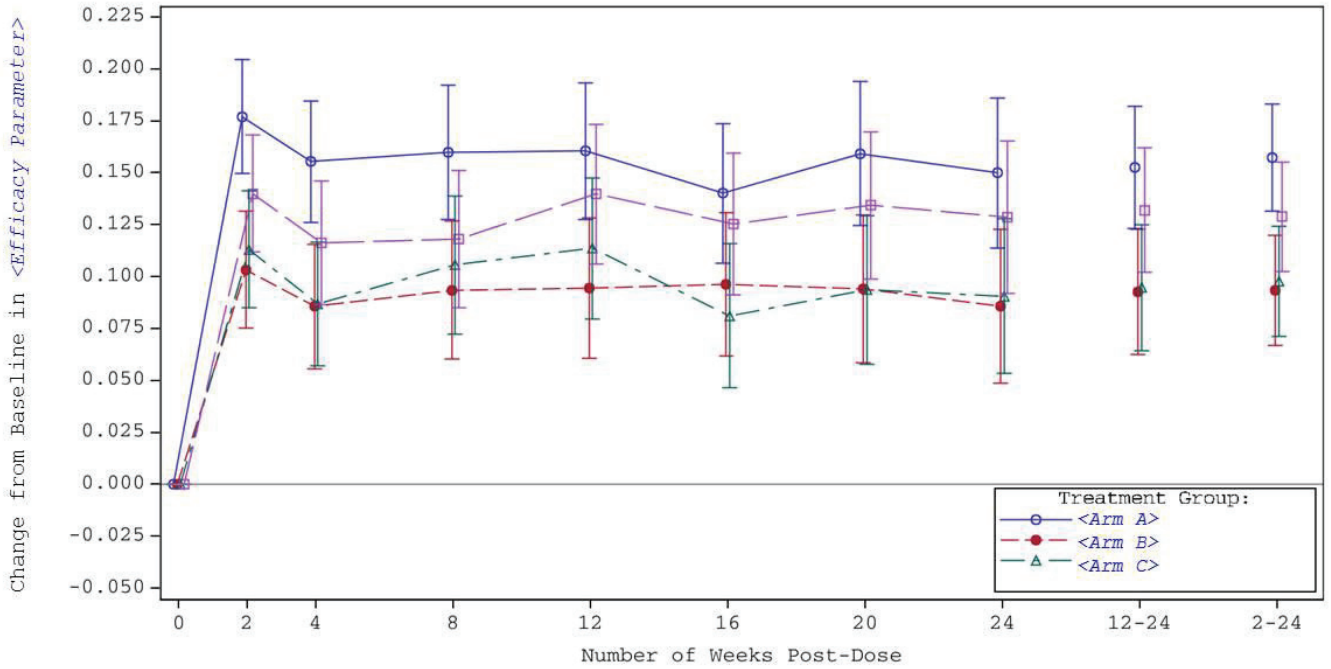
Notes to Programmer: Replace Number of Weeks Post-Dose with Number of Minutes Post-Dose.
Replace the treatment labels with 'AS MDI 180 µg', 'AS MDI 90 µg', 'Proventil 180 µg', 'Proventil 90 µg', and 'Placebo'.
Replace y-axis label with 'FEV_1 Change From Baseline'.

Figure 2.3.1.2 Treatment Differences From Placebo*: Change from Baseline in FEV_1 (L) ± 95% CI Over Time
Analysis Set: mITT Analysis Set



*Differences of active treatments vs. Plabebo.

Source: Table 2.3.1

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Notes to Programmer: Replace Number of Weeks Post-Dose with Number of Minutes Post-Dose.
Replace the treatment labels with 'AS MDI 180 µg', 'AS MDI 90 µg', 'Proventil 180 µg', and 'Proventil 90 µg'.
Replace y-axis label with 'FEV_1 Change From Baseline'.

Table 2.3.2 Time to Peak FEV_1
Analysis Set: mITT Analysis Set

	Placebo (N=xxx)	AS MDI 90 µg (N=xxx)	AS MDI 180 µg (N=xxx)	Proventil 90 µg (N=xxx)	Proventil 180 µg (N=xxx)
Subjects with a Post-Dose FEV_1, n(%)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Time to Peak FEV_1 (mins)					
Median (Min, Max)	x.x (x.x, x.x)	x.x (x.x, x.x)	x.x (x.x, x.x)	x.x (x.x, x.x)	x.x (x.x, x.x)
Median Difference (95% CI)					
Placebo (n=xxx)	Not Applicable	x.xxx (x.xxx, x.xxx)	x.xxx (x.xxx, x.xxx)	x.xxx (x.xxx, x.xxx)	x.xxx (x.xxx, x.xxx)
AS MDI 90 µg (n=xxx)		Not Applicable	x.xxx (x.xxx, x.xxx)	x.xxx (x.xxx, x.xxx)	x.xxx (x.xxx, x.xxx)
AS MDI 180 µg (n=xxx)			Not Applicable	x.xxx (x.xxx, x.xxx)	x.xxx (x.xxx, x.xxx)
Proventil 90 µg (n=xxx)				Not Applicable	x.xxx (x.xxx, x.xxx)

Time to Peak FEV_1 (mins) = (time of Peak FEV_1 – treatment administration time). Time to peak is calculated only for subjects with a post-dose FEV_1.
95% CI's of the median differences were calculated with Hodges-Lehmann CI's for paired observations.

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Notes to Programmer: Use data up to the last assessment for each visit.

Table 2.3.3 Percentage of Subjects Achieving a 12% or 15% Improvement in FEV_1 from Baseline Within 30 Minutes Post-Dose
Analysis Set: mITT Analysis Set

Reason for	Placebo (N=xxx) n (%)	AS MDI 90 µg (N=xxx) n (%)	AS MDI 180 µg (N=xxx) n (%)	Proventil 90 µg (N=xxx) n (%)	Proventil 180 µg (N=xxx) n (%)
Subjects Achieving 12% Improvement in FEV_1 from Baseline Within 30 Minutes of Dose	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Odds Ratio (95% CI)					
Placebo (n=xxx)	Not Applicable	x.xxx (x.xxx, x.xxx)	x.xxx (x.xxx, x.xxx)	x.xxx (x.xxx, x.xxx)	x.xxx (x.xxx, x.xxx)
AS MDI 90 µg (n=xxx)		Not Applicable	x.xxx (x.xxx, x.xxx)	x.xxx (x.xxx, x.xxx)	x.xxx (x.xxx, x.xxx)
AS MDI 180 µg (n=xxx)			Not Applicable	x.xxx (x.xxx, x.xxx)	x.xxx (x.xxx, x.xxx)
Proventil 90 µg (n=xxx)				Not Applicable	x.xxx (x.xxx, x.xxx)
Subjects Achieving 15% Improvement in FEV_1 from Baseline Within 30 Minutes of Dose	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Odds Ratio (95% CI)					
Placebo (n=xxx)	Not Applicable	x.xxx (x.xxx, x.xxx)	x.xxx (x.xxx, x.xxx)	x.xxx (x.xxx, x.xxx)	x.xxx (x.xxx, x.xxx)
AS MDI 90 µg (n=xxx)		Not Applicable	x.xxx (x.xxx, x.xxx)	x.xxx (x.xxx, x.xxx)	x.xxx (x.xxx, x.xxx)
AS MDI 180 µg (n=xxx)			Not Applicable	x.xxx (x.xxx, x.xxx)	x.xxx (x.xxx, x.xxx)
Proventil 90 µg (n=xxx)				Not Applicable	x.xxx (x.xxx, x.xxx)

N is the number of subjects with at least one post-dose FEV_1 assessment within 30 minutes of dose.
n is the number of subjects who did or did not achieve 12% or 15% improvement in FEV_1 from baseline within 30 minutes of dose.
The odds ratios are calculated from a a generalized mixed effects model with treatment as a fixed effect and the intercept for each subject as a random effect.

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Table 2.3.4 Time to Onset of 12% Improvement in FEV_1
Analysis Set: mITT Analysis Set

Note to the Programmer: Use shell for Table 2.3.2.
Replace footnote: Time to Onset of Response (minutes) = (time of first achievement of a 12% increase in FEV1 from baseline, within 30 minutes of dose – treatment administration time).

Table 2.3.5 Time to Onset of 15% Improvement in FEV_1
Analysis Set: mITT Analysis Set

Note to the Programmer: Use shell for Table 2.3.2.
Replace footnote: Time to Onset of Response (minutes) = (time of first achievement of a 15% increase in FEV1 from baseline, within 30 minutes of dose – treatment administration time).

Table 2.3.6 Duration of 12% Improvement in FEV_1
Analysis Set: mITT Analysis Set

			LS Mean Differences Between Treatments			
	Duration of Response (mins)	Placebo (N=xxx)	AS MDI 90 µg (N=xxx)	AS MDI 180 µg (N=xxx)	Proventil 90 µg (N=xxx)	Proventil 180 µg (N=xxx)
Subjects with a 12% increase in FEV_1 from baseline, within 30 minutes of dose, n(%)		xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Placebo (n=xxx)						
N	xx					
Mean	xxx.x					
SD	xxx.xx					
Median	x.x					
Min, Max	(x.x, x.x)					
LS Mean (SE)		Not Applicable	x.xxx (x.xxxx)	x.xxx (x.xxxx)	x.xxx (x.xxxx)	x.xxx (x.xxxx)
95% CI			(x.xxx, x.xxx)	(x.xxx, x.xxx)	(x.xxx, x.xxx)	(x.xxx, x.xxx)
P-value			x.xxxx	x.xxxx	x.xxxx	x.xxxx
AS MDI 90 µg (n=xxx)						
N	xx					
Mean	xxx.x					
SD	xxx.xx					
Median	x.x					
Min, Max	(x.x, x.x)					
LS Mean (SE)			Not Applicable	x.xxx (x.xxxx)	x.xxx (x.xxxx)	x.xxx (x.xxxx)
95% CI				(x.xxx, x.xxx)	(x.xxx, x.xxx)	(x.xxx, x.xxx)
P-value				x.xxxx	x.xxxx	x.xxxx
AS MDI 180 µg (n=xxx)						
N	xx					
Mean	xxx.x					
SD	xxx.xx					
Median	x.x					
Min, Max	(x.x, x.x)					
LS Mean (SE)				Not Applicable	x.xxx (x.xxxx)	x.xxx (x.xxxx)
95% CI					(x.xxx, x.xxx)	(x.xxx, x.xxx)
P-value					x.xxxx	x.xxxx

Proventil 90 µg (n=xxx)						
N	xx					
Mean	xxx.x					
SD	xxx.xx					
Median	x.x					
Min, Max	(x.x, x.x)					
LS Mean (SE)					Not Applicable	x.xxx (x.xxxx)
95% CI						(x.xxx, x.xxx)
P-value						x.xxxx
Proventil 180 µg (n=xxx)						
N	xx					
Mean	xxx.x					
SD	xxx.xx					
Median	x.x					
Min, Max	(x.x, x.x)					
LS Mean (SE)		Shown Above	Shown Above	Shown Above	Shown Above	Not Applicable
95% CI						
P-value						

Duration of response (mins) = (time of offset – time of onset) where onset is defined as a ≥ 12% improvement from baseline in FEV1 within the 30 minutes post dose. If a subject had a 2nd onset of response subsequent to achievement of offset, their data for that period was excluded from the duration of response analysis.
LS Means (SE), 95% CIs, and P-values are from a linear mixed effect model with a random subject effect for the correlation across periods and fixed effects for treatment, treatment sequence, and period.

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Notes to Programmer: Use data up to the last assessment for each visit.
The linear mixed model will be replaced with a distribution-free method (Hodges-Lehmann) as appropriate to the data.
Time to Onset of Response (minutes) = (time of first achievement of a 12% increase in FEV1 from baseline, within 30 minutes of dose – treatment administration time).
Time to Offset of Response: For responders only: (time of first assessment after achievement of response for which the increase from baseline in FEV_1 is < 15% (or 12%) – treatment administration time). If offset of FEV1 < 15% (or 12%) is not achieved and the last available assessment is ≥ 15% (or 12%), the time to offset will be defined as (the time of the last available assessment – treatment administration time. Thus, Offset of Response: For responders only: the 1st time point after achievement of response for which the increase from baseline in FEV1 is < 15% (or 12%). If offset is not achieved according to this definition, and the last available assessment is >= 15% (or 12%), offset will be defined as the time of the last available assessment.
Duration of response is defined n the table footnote above.:

Table 2.3.7 Duration of 12% Improvement in FEV_1: Subjects who Have Assessments at the 180- and 300-Minute Post-Dose Timepoints
Analysis Set: mITT Analysis Set

Table 2.3.8 Duration of 15% Improvement in FEV_1
Analysis Set: mITT Analysis Set

Notes to Programmer: Replace Duration footnote with: Duration of response (mins) = (time of offset – time of onset) where onset is defined as a ≥ 15% improvement from baseline in FEV1 within the 30 minutes post dose. If a subject had a 2nd onset of response subsequent to achievement of offset, their data for that period was excluded from the duration of response analysis.

Table 2.3.9 Duration of 15% Improvement in FEV_1: Subjects who Have Assessments at the 180- and 300-Minute Post-Dose Timepoints
Analysis Set: mITT Analysis Set

3. Safety

Adverse Events

Table 3.1.1 Overall Summary of Treatment-Emergent Adverse Events
Analysis Set: Safety Analysis Set

	Placebo (N=xxx)	AS MDI 90 µg (N=xxx)	AS MDI 180 µg (N=xxx)	Proventil 90 µg (N=xxx)	Proventil 180 µg (N=xxx)
	n (%) [Events]	n (%) [Events]	n (%) [Events]	n (%) [Events]	n (%) [Events]
Subjects With at Least One TEAE [a] [b]	xx (xx.x) [xxx]	xx (xx.x) [xxx]	xx (xx.x) [xxx]	xx (xx.x) [xxx]	xx (xx.x) [xxx]
Subjects With Serious TEAEs	xx (xx.x) [xx.x]	xx (xx.x) [xx.x]	xx (xx.x) [xx.x]	xx (xx.x) [xx.x]	xx (xx.x) [xx.x]
Subjects With TEAEs Related to Study Treatment [c]	xx (xx.x) [xxx]	xx (xx.x) [xxx]	xx (xx.x) [xxx]	xx (xx.x) [xxx]	xx (xx.x) [xxx]
Subjects With Serious TEAEs Related to Study Treatment [c]	xx (xx.x) [xx.x]	xx (xx.x) [xx.x]	xx (xx.x) [xx.x]	xx (xx.x) [xx.x]	xx (xx.x) [xx.x]
Subjects With TEAEs Leading to Early Discontinuation	xx (xx.x) [xx.x]	xx (xx.x) [xx.x]	xx (xx.x) [xx.x]	xx (xx.x) [xx.x]	xx (xx.x) [xx.x]
Deaths - All Causes	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

[a] TEAE = Treatment-Emergent Adverse Event
[a] Only adverse events on a Treatment Day were included in this table.
[c] Related = Yes or No.

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Table 3.1.2 Overall Summary of Treatment-Emergent Adverse Events Including Adverse Events on a Treatment Day or During the Washout or Follow-up Periods
Analysis Set: Safety Analysis Set

	Placebo (N=xxx)	AS MDI 90 µg (N=xxx)	AS MDI 180 µg (N=xxx)	Proventil 90 µg (N=xxx)	Proventil 180 µg (N=xxx)
	n (%) [Events]	n (%) [Events]	n (%) [Events]	n (%) [Events]	n (%) [Events]
Subjects With at Least One TEAE [a]	xx (xx.x) [xxx]	xx (xx.x) [xxx]	xx (xx.x) [xxx]	xx (xx.x) [xxx]	xx (xx.x) [xxx]
Subjects With Serious TEAEs	xx (xx.x) [xx.x]	xx (xx.x) [xx.x]	xx (xx.x) [xx.x]	xx (xx.x) [xx.x]	xx (xx.x) [xx.x]
Subjects With TEAEs Related to Study Treatment [b]	xx (xx.x) [xxx]	xx (xx.x) [xxx]	xx (xx.x) [xxx]	xx (xx.x) [xxx]	xx (xx.x) [xxx]
Subjects With Serious TEAEs Related to Study Treatment [b]	xx (xx.x) [xx.x]	xx (xx.x) [xx.x]	xx (xx.x) [xx.x]	xx (xx.x) [xx.x]	xx (xx.x) [xx.x]
Subjects With TEAEs Leading to Early Discontinuation	xx (xx.x) [xx.x]	xx (xx.x) [xx.x]	xx (xx.x) [xx.x]	xx (xx.x) [xx.x]	xx (xx.x) [xx.x]
Deaths - All Causes	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

[a] TEAE = Treatment-Emergent Adverse Event
[b] Related = Yes or No.

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Table 3.2.1 Treatment-Emergent Adverse Events by MedDRA Primary System Organ Class and Preferred Term
Analysis Set: Safety Analysis Set

System Organ Class Preferred Term	Placebo (N=xxx) n (%) [Events]	AS MDI 90 µg (N=xxx) n (%) [Events]	AS MDI 180 µg (N=xxx) n (%) [Events]	Proventil 90 µg (N=xxx) n (%) [Events]	Proventil 180 µg (N=xxx) n (%) [Events]
At Least One TEAE [a]	xx (xx.x) [xx]	xx (xx.x) [xx]	xx (xx.x) [xx]	xx (xx.x) [xx]	xx (xx.x) [xx]
System Organ Class 1	xx (xx.x) [xx]	xx (xx.x) [xx]	xx (xx.x) [xx]	xx (xx.x) [xx]	xx (xx.x) [xx]
Preferred Term 1	xx (xx.x) [xx]	xx (xx.x) [xx]	xx (xx.x) [xx]	xx (xx.x) [xx]	xx (xx.x) [xx]
Preferred Term 2	xx (xx.x) [xx]	xx (xx.x) [xx]	xx (xx.x) [xx]	xx (xx.x) [xx]	xx (xx.x) [xx]
System Organ Class 2	xx (xx.x) [xx]	xx (xx.x) [xx]	xx (xx.x) [xx]	xx (xx.x) [xx]	xx (xx.x) [xx]
Preferred Term 1	xx (xx.x) [xx]	xx (xx.x) [xx]	xx (xx.x) [xx]	xx (xx.x) [xx]	xx (xx.x) [xx]
Preferred Term 2	xx (xx.x) [xx]	xx (xx.x) [xx]	xx (xx.x) [xx]	xx (xx.x) [xx]	xx (xx.x) [xx]
Etc.…					

[a] TEAE = Treatment-Emergent Adverse Event.

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Table 3.2.2 Treatment-Emergent Adverse Events by MedDRA Primary System Organ Class and Preferred Term Including Events Occurring During the Washout or Follow-up Periods: Sensitivity Analysis
Analysis Set: Safety Analysis Set

Notes to Programmer: Same as Table 3.2.1, however, AEs that occur during the Washout Period or Follow-up periods are attributed to the treatment given in the preceding Treatment Period. Add the following footnote: "AEs that occur during the Washout or Follow-up periods are attributed to the treatment given in the preceding Treatment Period."

Table 3.2.3 Treatment-Emergent Adverse Events Occurring in >=2% of Subjects in a Treatment by Descending Frequency
Analysis Set: Safety Analysis Set

Notes to Programmer: Sort preferred terms by descending frequency of number of events across All Subjects. Use the format of Table 3.2.1, but delete the "At Least One" row from this Table. SOCs will not be used in this Table.

Table 3.2.4 Non-serious Treatment-Emergent Adverse Events Occurring in >=5% of Subjects in a Treatment by MedDRA Primary System Organ Class and Preferred Term
Analysis Set: Safety Analysis Set

Notes to Programmer: use the format of Table 3.2.1.

Table 3.3 Treatment-Related Treatment-Emergent Adverse Events by MedDRA Primary System Organ Class and Preferred Term
Analysis Set: Safety Analysis Set

```
[a]  Related = Yes or No.

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Notes to Programmer: use the format of Table 3.2.1.

Table 3.4 Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation by MedDRA Primary System Organ Class and Preferred Term
Analysis Set: Safety Analysis Set

```
[a]  A TEAE leading to treatment discontinuation is an AE with 'Action Taken' = 'Drug withdrawn', or 'Outcome' = 'Fatal',
     or 'Death' as reason for Seriousness on Adverse Event' CRF.

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Notes to Programmer: use the format of Table 3.2.1.

Table 3.5 Listing of Adverse Events Leading to Permanent Discontinuation of Study Treatment
Analysis Set: All Subjects Randomized

Subject ID (Age/ Gender/ Race) [a]	Primary System Organ Class	AE Verbatim (Preferred Term)	Treat. Emerg.	Event Serious	Onset Date (Study Day) [b]	Duration of Event [c]	Severity	Relation -ship	Action	AE Treated	Outcome (Death)	Study Day Resolved/ Death [b]
Treatment: AS MDI 180 µg, AS MDI 90 µg, Placebo, Proventil 180 µg, or Proventil 90 µg												
Center # (Investigator): Center ### (xxxxxxxxxx)												
xxxxxx (54/F/W)	xxx xxx xxxxx	AE 1 (xxxxxxxxxx)	Yes	No	YYYY-MM-DD (T1_2)		Moderate	Not Related	Dose not changed	No	Recovering/Resolving (No)	
	xxx xxx xxxx	AE 2 (xxxxxxxxxx)	Yes	Yes	YYYY-MM-DD (T2_P1)	xx	Moderate	Related	Drug Interrupted	Yes	Recovered /Resolved (Yes)	T2_P3
	…	…										

Race: A=Asian, AIAN=American Indian or Alaska Native, B=Black or African American, NHPI=Native Hawaiian or Other Pacific Islander, O=Other W=White. Gender: F=Female, M=Male.
SOC = System Organ Class.
[a] # indicates that it could not be determined whether the AE had onset during study treatment.
[b] A negative number for study day denotes the number of days prior to the start of study treatment. Otherwise, Study Day is Date – Date of dose in the Period + 1. Tx = Period. Tx_y = Period and Day within Period. Pxx = Days after dose in the last Treatment Period.
On Study Day 1, an @ indicates that event started before study drug administration.
On Study Day 1, @@ indicates that event started after study drug administration.
[c] Duration of Event = Stop Day - Onset Day + 1

Report generated by program: PT007001/sasdir/programs/statout/t0305.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer: Sort by Actual Treatment, Center, Subject ID, Primary System Organ Class, and Onset Day of AE. Page by Treatment and not by Treatment and Center.

Table 3.6.1 Serious Adverse Events by MedDRA Primary System Organ Class and Preferred Term
Analysis Set: Safety Analysis Set

Notes to Programmer: Same as Table 3.2.1.

Table 3.6.2 Serious Adverse Events by MedDRA Primary System Organ Class and Preferred Term Including Events Occurring During the Washout and Follow-up Period: Sensitivity Analysis
Analysis Set: Safety Analysis Set

Notes to Programmer: Same as Table 3.2.1, however, SAEs that occur during the Washout or Follow-up periods are attributed to the treatment given in the preceding Treatment Period. Add the following footnote: "SAEs that occur during the Washout or Follow-up periods are attributed to the treatment given in the preceding Treatment Period."

Table 3.7.1 Listing of Serious Adverse Events (SAEs)
Analysis Set: All Subjects Screened

Subject ID	Age (yrs)/ Gender/ Race	Primary System Organ Class	SAE Verbatim (Preferred Term)	Reason for Being Serious (Day) [a]	Treat. Emerg. [b]	Onset Day [b] (Day of Most Recent Dose)	Duration of Event [c]	Severity/ Relation-ship	Action/ (Outcome) (AE Treated)	Study Day Resolved [a]
Treatment: AS MDI 180 µg, AS MDI 90 µg, Placebo, Proventil 180 µg, or Proventil 90 µg										
Center # (Investigator): Center ### (xxxxxxxxxx)										
xxxxxx	70/F/W	xxxx xxx xx xxxx	xxx xxx xxxxx xxxxxxx (xxxxxxxxxxxxxxxxxx)	Hospitalization / prolongation of existing Hospitalization (T1_1-Tx_y)	Yes	5 (T2_P1)	4	Moderate / Not Related	None (Recovered/Resolved) (Yes) Drug Interrupted, Date Stopped: YYYY-12-07; AE abated: Yes; Date restarted: YYYY_12_08: AE reoccur? Yes	Tx_8

Race: A=Asian, AIAN=American Indian or Alaska Native, B=Black or African American, NHPI=Native Hawaiian or Other Pacific Islander, O=Other W=White. Gender: F=Female, M=Male.
[a] A negative number for study day denotes the number of days prior to the start of study treatment. Otherwise, Study Day is Date - Date of dose in the Period + 1. Tx = Period. Tx_y = Period and Day within Period. Pxx = Days after dose in the last Treatment Period.
On Study Day 1, an @ indicates that event started before study drug administration.
On Study Day 1, @@ indicates that event started after study drug administration.
[b] # indicates that it could not be determined whether the AE had onset during study treatment.
[c] Duration of Event = Stop Day - Onset Day + 1

Report generated by program: PT007001/sasdir/programs/statout/t030801.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer:
Sort by Actual Treatment, Center, Subject ID, Primary System Organ Class Preferred Term, and Onset Day.
If Reason for Seriousness is Hospitalization or Prolongation of Existing Hospitalization, also present in parentheses the days subject admitted into and discharged from Hospital "(Day xx – Day xx)".
If the Reason for Seriousness is death, also present the day of death.

Table 3.7.2 Listing of SAE-Specific Report Information
Analysis Set: Screened

Subject ID	Diagnosis, Details and Relevant Diagnostic Tests	Last Treatment and Date (YYYY-MM-DD)	Date of SAE Onset (YYYY-MM-DD) And Most Recent Dose of Treatment Prior to Onset of SAE	Serious Reason (YYYY-MM-DD)	Action Taken With Study Drug	Severity/ Relationship/ (Outcome) (YYYY-MM-DD)	SAE Treated
Treatment: AS MDI 180 µg, AS MDI 90 µg, Placebo, Proventil 180 µg, or Proventil 90 µg							
Center # / (Investigator): ### / (xxxxxxxxxx)							
xxxx	Diagnosis: xxxxxxxxxxxxxxxxxxxxxx Details: signs, symptoms, time course, and relevant medical history. Relevant Diagnostic Tests: Confirmatory procedures and Results, if any.	C 2015-07-28	2015-07-24 YYYY-MM-DD	Death (YYYY-MM-DD) Autopsy: yes or no Life-threatening Hospitalization or prolongation of existing hospitalization (YYYY-MM-DD-YYYY-MM-DD) A persistent or significant disability/incapacity Congenital anomaly/birth defect A significant medical event that requires medical or surgical intervention to prevent one of the serious outcomes listed above.	None Drug Interrupted (Stopped: YYYY-MM-DD SAE Abated: Yes/No Treatment Restarted: YYYY-MM-DD SAE Reoccur: Yes/no) Permanently Withdrawn (YYYY-MM-DD)	Moderate / Related / (Recovered/Resolved) (2015-07-27)	Yes/No

Notes to Programmer: Sort by Center, Subject ID, and Onset Day of SAE. Move 'Center' row header to the next page whenever there is not enough room on current page to fit at least one row of data underneath this header. In order for the SAE-Specific Report Information to be listed, it will need to be included in the SDTM data sets.

Table 3.8 Treatment Related Serious Adverse Events by MedDRA Primary System Organ Class and Preferred Term
Analysis Set: Safety Analysis Set

[a] Related = Yes or No.

Notes to Programmer: Same as Table 3.2.1.

Table 3.9.1 TEAEs by Primary System Organ Class, Preferred Term, and Highest Severity – Placebo
Analysis Set: Safety Analysis Set

Primary System Organ Class Preferred Term	Placebo (N=xxx) Mild n (%)	 Moderate n (%)	 Severe n (%)	 Any Severity n (%)
At Least One TEAE	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
System Organ Class 1	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Preferred Term 1	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Preferred Term 2	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
System Organ Class 2	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Preferred Term 1	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Preferred Term 2	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
….				

Only the highest severity is counted for multiple occurrences of the same adverse event in one individual.

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Table 3.9.2 TEAEs by Primary System Organ Class, Preferred Term, and Highest Severity – AS MDI 90 µg
Analysis Set: Safety Analysis Set

Table 3.9.3 TEAEs by Primary System Organ Class, Preferred Term, and Highest Severity – AS MDI 180 µg
Analysis Set: Safety Analysis Set

Table 3.9.4 TEAEs by Primary System Organ Class, Preferred Term, and Highest Severity – Proventil 90 µg
Analysis Set: Safety Analysis Set

Table 3.9.5 TEAEs by Primary System Organ Class, Preferred Term, and Highest Severity – Proventil 180 µg
Analysis Set: Safety Analysis Set

Table 3.10 Listing of Deaths
Analysis Set: All Subjects Screened

Subject ID	Treatment Sequence	Study Day of Dose of Last Treatment Prior to Death [a]	Days on Treat-ment	Date and Time (YYYY-MM-DD) (24 h clock) of Death	Days Since Dose at Time of Death [b]	Adverse Event Preferred Term/Verbatim Term
Study Center # / (Investigator): ### / (xxxxxxxxxx)						
xxxxx	x/x	TRT A Day x (YYYY-MM-DD)	1	YYYY-MM-DD hh:mm	x	Preferred Term/AE verbatim

Treatment: A = Placebo, B = AS MDI 90 µg, C = AS MDI 180 µg, D = Proventil 90 µg, E = Proventil 180 µg, - = Not Treated.
This includes all subjects who died while on study and up to 30 Days after final treatment dose.
TRT = Treatment.
[a] Study Day of Dose for Treatment = Study Day 1.
[b] Days since Last Dose = Date of death – Date of last dose of study treatment + 1.

Report generated by program: PT007001/sasdir/programs/statout/t0313.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer: For TRT N, N is the treatment period number of the last treatment received by the subject prior to the death.
Sort by Study Center and Subject within Study Center. Move 'Study Center/Inv' row header to the next page whenever there is not enough room on current page to fit at least one row of data underneath this header.

Vital Signs

Table 3.11.1 Vital Sign Parameters
Analysis Set: Safety Analysis Set

Parameter (unit)	Visit/Timepoint	Statistic	Placebo (N=xxx)	AS MDI 90 µg (N=xxx)	AS MDI 180 µg (N=xxx)	Proventil 90 µg (N=xxx)	Proventil 180 µg (N=xxx)
Parameter 1 (unit)	Screening (Visit 1)	Actual Value:					
		n	xxx	xxx	xxx	xxx	xxx
		Mean	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
		SD	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
		Median	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
		Minimum	x.xx	x.xx	x.xx	x.xx	x.xx
		Maximum	x.xx	x.xx	x.xx	x.xx	x.xx
	Baseline (Visit 2 Pre-Dose)	Actual Value:					
		n	xxx	xxx	xxx	xxx	xxx
		Mean	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
		SD	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
		Median	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
		Minimum	x.xx	x.xx	x.xx	x.xx	x.xx
		Maximum	x.xx	x.xx	x.xx	x.xx	x.xx
		Change From Baseline:					
		n	xxx	xxx	xxx	xxx	xxx
		Mean	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
		SD	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
		Median	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
		Minimum	x.xx	x.xx	x.xx	x.xx	x.xx
		Maximum	x.xx	x.xx	x.xx	x.xx	x.xx

For parameters Height, Weight, and BMI, only include Screening. For SPB, DBP, and Heart Rate include Screening, Baseline (Visit 2 Pre-Dose), Visit 2 (Post-Dose), Visit 3 (Pre-Dose), Visit 3 (Post-Dose), Visit 4 (Pre-Dose), Visit 4 (Post-Dose), Visit 5 (Pre-Dose), Visit 5 (Post-Dose), Visit 6 (Pre-Dose), Visit 6 (Post-Dose), and End of Treatment.

Baseline is defined as the last pre-dose measurement taken prior to dosing on Day 1 of a treatment period.
End of Treatment is defined as the last non-missing on treatment assessment available for the timepoint.

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Notes to Programmer:
Repeat the parameter at the beginning of each page under column header. Repeat for all parameters.

4. Subject Data Listings

4.1 Subject Discontinuations/Completions

Listing 1.1 Study Centers
Analysis Set: All Subjects Screened

Center	Investigator	Location
xxxxxx	xxxxxxxxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxx City Country
xxxxxx	xxxxxxxxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxx City Country
xxxxxx	xxxxxxxxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxx City Country

Source: xxxxxxx.sas7bdat

Report generated by program: /sasdir/programs/statout/l0101.sas Version YYYY-MM-DD xx:xx (Page n of N)

Listing 1.2 Subject Disposition and Demographic Data
Analysis Set: All Subjects Screened

			Smoking History						
Subject ID (Treatment Sequence)	Age (yrs)[a]/ Gender (Race/Ethnicity)	Height(cm)/ Weight (kg)/ BMI (kg/m^2)	Smoking Status [b]	Number of Weeks Since Day Quit	Number of Years Smoked	Average Number of Cigarettes Smoked Per Day	Number of Pack Years Smoked [c]	Randomized? (Study Day) [d]	Subject Study Status (Date of Last Dose [Study Day)} (Follow-up Call? Date) Date of Death [e]
Center # (Investigator): Center ### (xxxxxxxxxx)									
Xxxxxx (A/B/E/C/D)	Xx/M (x/xx)	xxx.x/ xx.x/ xx.x	Former Smoker	xx.x	xx	xx	xx.x	Yes/No (xx)	Completed Study (YYYY-MM-DD [xxx]) (Yes YYYY-DD-MM) NA
Xxxxxx (A/E/-/-/-)	Xx/M (x/xx)	xxx.x/ xx.x/ xx.x	Former Smoker	xx.x	xx	xx	xx.x	Yes/No (xx)	Discontinued Investigator's Decision (YYYY-MM-DD [Tx_y]) (No)
Xxxxxx (B/A/C/E/-)	Xx/M (x/xx)	xxx.x/ xx.x/ xx.x	Former Smoker	xx.x	xx	xx	xx.x	Yes/No (xx)	Discontinued Subject Lost to Follow up (YYYY-MM-DD [Tx_y]) (No)
Xxxxxx (B/C/-/-/-)	Xx/M (x/xx)	xxx.x/ xx.x/ xx.x	Non Smoker	xx.x	xx	xx	xx.x	No (NA)	Discontinued Investigator's Decision (YYYY-MM-DD [Tx_y]) (No)
Xxxxxx (A/B/E/C/D)	Xx/M (x/xx)	xxx.x/ xx.x/ xx.x	Former Smoker	xx.x	xx	xx	xx.x	No (NA)	Discontinued Adverse Event (YYYY-MM-DD [Tx_y]) (No) Death: YYYY-MM-DD

Treatment: A = Placebo, B = AS MDI 90 µg, C = AS MDI 180 µg, D = Proventil 90 µg, E = Proventil 180 µg, - = Not Treated.
Race: A=Asian, AIAN=American Indian or Alaska Native, B=Black or African American, NHPI=Native Hawaiian or Other Pacific Islander, O=Other W=White. Ethnicity: H=Hispanic, NH=Not Hispanic, UNK=Unknown, NR=Not Reported. Gender: F=Female, M=Male.
[a] Age = integer part of ((Visit 1 date – Birth date)/365.25)
[b] Former Smoker is defined as those who have stopped smoking for at least 6 months prior to first Screening Visit.

[c] Number of pack years smoked = (number of cigarettes per day / 20) x number of years smoked.
[d] Study Day of randomization = date of randomization – first dose of study treatment
[e] The Date of Discontinuation is the later of the last visit date, the date of the last dose of study medication, or the date of last contact for subjects lost-to-followup. For subjects not randomized, date of discontinuation Study Day is the last visit date - date of Screening Visit 1; for treated subjects, Study Day is the date of discontinuation - date of first dose of study treatment + 1.

Source: xxxxxxx.sas7bdat

Report generated by program: PT007001/sasdir/programs/statout/l0102.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer:
Sort by Center, and Subject ID within Center.
Last Contact Date on the End of Treatment CRF is date of last contact.
If Race = Other, concatenate the specified race after 'O' within parenthesis, e.g., "O (specified)".
Move 'Study Center/Inv' row header to the next page whenever there is not enough room on current page to fit at least one row of data underneath this header.

Listing 1.3 Randomized Treatment, Actual Treatment, and Duration of Treatment
Analysis Set: All Subjects Randomized

Subject ID	Randomized Treatment Sequence (Actual Treatment Sequence)	Period 1 Treatment (Start Study Day and time – End Study Day and time)/ Duration (days)/ Washout Length (days) [a]	Period 2 Treatment (Start Study Day and time – End Study Day and time)/ Duration (days)/ Washout Length (days) [a]	Period 3 Treatment (Start Study Day and time – End Study Day and time)/ Duration (days)/ Washout Length (days) [a]	Period 4 Treatment (Start Study Day and time – End Study Day and time)/ Duration (days)/ Washout Length (days) [a]	Period 5 Treatment (Start Study Day and time – End Study Day and time)/ Duration (days)/ Washout Length (days) [a]	Study Day of First and Last Dose of Study treatment in the study
Study Center # / (Investigator): ### / (xxxxxxxxxx)							
xxxxx	A/B/E/C/D (A/B/E/C/D)	AS MDI 180 µg (xxx hh:mm - xxx hh:mm)/ 29/ (7)	AS MDI 90 µg (xxx hh:mm - xxx hh:mm)/ 25/ (7)	Placebo (xxx hh:mm - xxx hh:mm)/ 25/ (7)	Proventil 180 µg (xxx hh:mm - xxx hh:mm)/ 25/ (7)	Proventil 90 µg (xxx hh:mm - xxx hh:mm)/ 25/ (7)	xxx – xxx
xxxxx	B/A/C/E/- (B/A/C/E/-)	Proventil 180 µg (xxx hh:mm - xxx hh:mm)/ 29/ (7)	AS MDI 180 µg (xxx hh:mm - xxx hh:mm)/ 25/ (7)	Proventil 90 µg (xxx hh:mm - xxx hh:mm)/ 25/ (7)	Placebo (xxx hh:mm - xxx hh:mm)/ 25/ (7)		xxx – xxx
xxxxx	A/B/E/C/D (A/E/-/-/-)	AS MDI 90 µg (xxx hh:mm - xxx hh:mm)/ 25/ (7)	Placebo (xxx hh:mm - xxx hh:mm)/ 25/ (7)				xxx – xxx

Treatment: A = Placebo, B = AS MDI 90 µg, C = AS MDI 180 µg, D = Proventil 90 µg, E = Proventil 180 µg, - = Not Treated.
Study Day of First Dose of Drug in the study is defined as the study day of the first dose of study medication in the study (Study Day 1) which is the study day of Treatment 1 Day 1 from the Study Drug Administration CRF.
Study Day of the Last Dose of Study Drug in the study is defined as the Study Day of the last dose of study medication in the study - Study Day of first dose of study medication in the study + 1.
NA = not applicable
Time is 24 hour clock time.
[a] Washout length (days) for the subject's last period is the number of days between the follow-up telephone call and the dose date in the last period. The duration of a washout (or follow-up) period = (start date of subsequent treatment (or follow-up telephone call) - stop date of previous study treatment.

Source: xxxxxxx.sas7bdat

Report generated by program: PT007001/sasdir/programs/statout/l0103.sas Version YYYY-MM-DD xx: (Page n of N)

Notes to Programmer: Sort by Center and Subject within Center. Move 'Study Center/Inv' row header to the next page whenever there is not enough room on current page to fit at least one row of data underneath this header.

Listing 1.4 Reasons Subjects Were Not Randomized
Analysis Set: All Subjects Not Randomized

Subject ID	Date of Screening	Age (yrs)	Gender	Race	Reason Not Randomized
Center # (Investigator): Center ### (xxxxxxxxxx)					
xxxxxx	YYYY-MM-DD	xx	Male	W	xxxxxxxxxxxxxxx (Inclusion Criterion #n)
xxxxxx	YYYY-MM-DD	xx	Female	W	xxxxxxxxxxxxxx (Inclusion Criterion #n)
xxxxxx	YYYY-MM-DD	xx	Male	W	xxxxxxxxxxxxxx (Inclusion Criterion #n)
xxxxxx	YYYY-MM-DD	xx	Male	W	xxxxxxxxxxxxxx (Inclusion Criterion #n)
Xxxxxx	YYYY-MM-DD	Xx	Female	W	xxxxxxxxxxxxxx (Inclusion Criterion #n)

Race: A=Asian, AIAN=American Indian or Alaska Native, B=Black or African American, NHPI=Native Hawaiian or Other Pacific Islander, O=Other W=White.

Source: xxxxxxx.sas7bdat

Report generated by program: PT007001/sasdir/programs/statout/l0104.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer:
Sort by Center and Subject ID within Center.
If Race = Other ("O"), concatenate the specified race after 'O' within parenthesis, e.g., "e.g., "O: xxxxxx".
Move 'Study Center/Inv' row header to the next page whenever there is not enough room on current page to fit at least one row of data underneath this header. If country is shown, move country to the next page if there is not enough room.

4.2 Protocol Deviations

Listing 2 Violation of Inclusion/Exclusion Criteria
Analysis Set: All Subjects Randomized

					Eligibility			
Subject ID	Treatment Sequence	Age (yrs)/ Gender (Race) [a]	Informed Consent Signed	Informed Consent Study Day [a]	Visit	Study Day [a]	Inclusion/ Exclusion Criteria Satisfied	Type of Failed Criteria
Center # (Investigator): Center ### (xxxxxxxxxx)								
xxxxxx	A/B/E/C/D	xx/M (BA)	Yes	-xx	Visit 1	-xx	No	Inclusion

Treatment: A = Placebo, B = AS MDI 90 µg, C = AS MDI 180 µg, D = Proventil 90 µg, E = Proventil 180 µg, - = Not Treated.
Race: A=Asian, AIAN=American Indian or Alaska Native, B=Black or African American, NHPI=Native Hawaiian or Other Pacific Islander, O=Other W=White. Gender: F=Female, M=Male.
[a] A negative number for study day denotes the number of days prior to the start of study treatment.

Source:xxxxxxx.sas7bdat

Report generated by program: PT007001/sasdir/programs/statout/l02.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer:
If Race = Other ("O"), concatenate the specified race after 'O' within parenthesis, e.g., "O (specified)".
Sort by Center, and Subject ID within Center.
Move 'Study Center/Inv' row header to the next page whenever there is not enough room on current page to fit at least one row of data underneath this header.

4.3 Screening Lung Function and Reversibility

Listing 3 Screening Lung Function and Ventolin HFA Reversibility
Analysis Set: All Subjects Randomized

Subject ID	Treatment Sequence	Age (yrs) /Gender (Race) [a]	Visit	Effort Date	Time of Ventolin HFA Dose (24 h clock)	Pre-Dose FEV_1 (L)	Pre-Dose FVC (L)	Pre-Dose PEFR (L/min)	Post-Dose FEV_1 (L)	Post-Dose FVC (L)	Post-Dose PEFR (L/min)	Reversibility %
Center # (Investigator): Center ### (xxxxxxxxxx)												
	A/B/E/C	xx/x			xx:xx	x.xxx	x.xxx	xxx.xxx	x.xxx	x.xxx	xxx.xxx	
xxxxx	/D	(xxx)	1	YYYY-MM-DD								
			1a	YYYY-MM-DD	xx:xx	x.xxx	x.xxx	xxx.xxx	x.xxx	x.xxx	xxx.xxx	xx.x
			1b	YYYY-MM-DD		x.xxx	x.xxx	xxx.xxx	x.xxx	x.xxx	xxx.xxx	xx.x
	B/A/C/E	xx/x			xx:xx	x.xxx	x.xxx	xxx.xxx	x.xxx	x.xxx	xxx.xxx	xx.x
xxxxx	/-	(xxx)	1	YYYY-MM-DD								
	A/B/E/C	xx/x				x.xxx	x.xxx	xxx.xxx	x.xxx	x.xxx	xxx.xxx	xx.x (V)
xxxxx	/D	(xxx)	1	YYYY-MM-DD								

Treatment: A = Placebo, B = AS MDI 90 µg, C = AS MDI 180 µg, D = Proventil 90 µg, E = Proventil 180 µg, - = Not Treated.
Race: A=Asian, AIAN=American Indian or Alaska Native, B=Black or African American, NHPI=Native Hawaiian or Other Pacific Islander, O=Other W=White. Gender: F=Female, M=Male.
NA = not applicable.

Source: xxxxxxx.sas7bdat

Report generated by program: PT007001/sasdir/programs/statout/l03.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer: Sort by Center, and Subject ID within Center. Move 'Study Center/Inv' row header to the next page whenever there is not enough room on current page to fit at least one row of data underneath this header.

4.4 Baseline Characteristics

Listing 4.1 Asthma Diagnosis
Analysis Set: All Subjects Randomized

Subject ID	Treatment Sequence	Age (yrs)/Gender/Race [a]	Asthma First Diagnosed	
			Date [s]	Years Prior to First Dose [b]
Center # (Investigator): Center ### (xxxxxxxxxx)				
xxxxxx	A/B/E/C/D	xx / Male/ xxxx	YYYY-MM	x.x
		xx / Female / xxxx	YYYY-06*	xx.x

Treatment: A = Placebo, B = AS MDI 90 µg, C = AS MDI 180 µg, D = Proventil 90 µg, E = Proventil 180 µg, - = Not Treated.
Race: A=Asian, AIAN=American Indian or Alaska Native, B=Black or African American, NHPI=Native Hawaiian or Other Pacific Islander, O=Other W=White. Gender: F=Female, M=Male.
[a] Missing month of Date Asthma First Diagnosed was imputed as June, or the month in which 1st was the latest before informed consent date; '*' indicates the month displayed was imputed.
[b] Months Prior to First Dose When Asthma was First Diagnosed = (Date of First Dose of Study treatment in the study - Date Asthma First Diagnosed)/30.4375. Day of Diagnosis was imputed for all subjects as the 1st of the month.

Source: xxxxxxx.sas7bdat

Report generated by program: PT007001/sasdir/programs/statout/l0401.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer: Sort by Center and Subject ID within Center. Move 'Study Center/Inv' row header to the next page whenever there is not enough room on current page to fit at least one row of data underneath this header.

Listing 4.2 Medical and Surgical History
Analysis Set: All Subjects Randomized

Subject ID	Treatment Sequence	Age (yrs)/ Gender (Race) [a]	Category	System Organ Class	Diagnosis or Surgery/ (Preferred Term)	Onset Date	Onset Day [a]	Still Present?	End Date (Year/ Month)	End Day [b]
Center # (Investigator): Center ### (xxxxxxxxxx)										
xxxxxx	A/B/E/C/D	xx/x (xxxx)	Drug Allergy	xxxxxxxx	xxxxx/(xxxx)	YYYY-MM	-xxx	No	YYYY-MM	xxx
			Malignancy	xxxxxx	xxxxx/(xxxx)	YYYY-MM	-xxx	No	YYYY-MM	xxx
xxxxxx	B/A/C/E/-	xx/x (xxxx)	CNS/Neurological	xxxxxxxxxxxxxxx	xxxxx/(xxxx)	YYYY-MM	-xxx	No	YYYY-MM	xxx
			Endocrine/Metabolic	xxxxxxxxxx	xxxxx/(xxxx)	YYYY-MM	-xxx	Yes		Ongoing
xxxxxx	A/B/E/C/D	xx/x (xxxx)	Eyes/Ear/Nose/Throat	xxxxxxxxxxx	xxxxx/(xxxx)	YYYY-MM	-xx	No	YYYY-MM	xxx
xxxxxx	B/A/C/E/-	xx/x (xxxx)	Other	xxxxxxxxxx	xxxxx/(xxxx)	YYYY-MM	-xxx	No	YYYY-MM	xxx

Treatment: A = Placebo, B = AS MDI 90 µg, C = AS MDI 180 µg, D = Proventil 90 µg, E = Proventil 180 µg, - = Not Treated.
Race: A=Asian, AIAN=American Indian or Alaska Native, B=Black or African American, NHPI=Native Hawaiian or Other Pacific Islander, O=Other W=White. Gender: F=Female, M=Male.
[a] Onset Day=Onset date of condition – date of the first dose of study treatment. Day was imputed as 1st of the month. Missing month was imputed as June, or the month in which 1st was the latest before informed consent date; '*' indicates the month displayed was imputed.
[b] End Day=End date of condition – date of the first dose of study treatment. Day was imputed as 1st of the month. Missing month was imputed as June, or the month in which 1st was the latest before informed consent date; '*' indicates the month displayed was imputed.

Source: xxxxxxx.sas7bdat

Report generated by program: PT007001/sasdir/programs/statout/l0402.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer: Sort by Center, Subject ID, and Onset Day. Move 'Study Center/Inv' row header to the next page whenever there is not enough room on current page to fit at least one row of data underneath this header.

Listing 4.3 Screening Reproductive Status and Pregnancy Test Results
Analysis Set: All Subjects Randomized

Subject ID	Treatment Sequence	Age (yrs) /Gender (Race)	Screening Female Reproductive Status	If Subject is a WOCBP, Was Pregnancy Test Performed?	Pregnancy Test				
					Visit [a]	Visit Date	Type of Pregnancy Test	Study Day of Test [b]	Result
Center # (Investigator): Center ### (xxxxxxxxxx)									
xxxxxx	A/B/E/C/D	xx/F/(xxx x)	Woman of Non-Childbearing Potential (Non-WOCBP)		Visit 1	YYYY-MM-DD	Not Done	NA	NA
xxxxxx	B/A/C/E/-	xx/F/(xxx x)	Woman of Childbearing Potential (WOCBP)	Yes	Visit 2	YYYY-MM-DD	Serum Pregnancy Test	xxx	Positive

Treatment: A = Placebo, B = AS MDI 90 µg, C = AS MDI 180 µg, D = Proventil 90 µg, E = Proventil 180 µg, - = Not Treated.
Race: A=Asian, AIAN=American Indian or Alaska Native, B=Black or African American, NHPI=Native Hawaiian or Other Pacific Islander, O=Other W=White. Gender: F=Female, M=Male.
[a] Pregnancy testing at Visit 2 was done prior to randomization.
[b] Study Day is defined as date of test – date of the first dose of study treatment.

Source: xxxxxxx.sas7bdat

Report generated by program: PT007001/sasdir/programs/statout/l0403.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer:
Sort by Center, Investigator, Subject ID within Center, Visit, and Study Day of Pregnancy Test. List female subjects only.
Move 'Study Center/Inv' row header to the next page whenever there is not enough room on current page to fit at least one row of data underneath this header.

Listing 4.4 Prior, Concomitant, and Post-Treatment Asthma Medications
Analysis Set: All Subjects Randomized

Subject ID (Treatment Sequence)	Medication Verbatim Term (Preferred Term) (ATC Term)	Dose/ Unit/ Route/ Frequency	Reason for Use	Begin Date (YYYY-MM-DD)	Stop Date (YYYY-MM-DD)	Ongoing	Duration (Days)	Study Day Begin Day [a]	Study Day Stop Day [a]	Prior/ Concomitant/Post-Treatment
Center # (Investigator): Center ### (xxxxxxxxxx)										
1001 (A/B/E/C/D)	xxxxxxxxxxx (xxxxxx) (xxxxxx)	90/ MCG/ IH/ PRN	Asthma Exacerbation # xxx	2008-XX-XX		Yes		-22		Yes/Yes/No
			Other, <specify>	2008-XX-XX		Yes		-22		Yes/Yes/No

Treatment: A = Placebo, B = AS MDI 90 µg, C = AS MDI 180 µg, D = Proventil 90 µg, E = Proventil 180 µg, - = Not Treated.

All Asthma-related medications taken within 30 days of Screening and while on study are listed.
Medications were considered to be prior medications if taken prior to the start of study treatment. Medications were considered concomitant if they were reported as being taken at any point from the start of randomized study treatment to the last date of study treatment. Medications with an onset date on or after the last dose of study treatment were considered post-treatment medications.
All subjects were allowed sponsor provided Ventolin HFA, and Pulmicort if previously using regularly scheduled ICS or ICS/LABA, during the Screening period, and Atrovent and/or Pulmicort during the treatment period which were reported on the Concomitant Medications CRF.
XX = Unknown month or day.
[a] A negative number for study day denotes the number of days prior to the start of study treatment. Pxx = Days after dose in last Treatment Period.

Sources: xxxxxxx.sas7bdat

Report generated by program: PT007001/sasdir/programs/statout/l0404.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer:
Sort by Center, Subject ID, Preferred Term, and Begin Date of Asthma medication. Show Anatomic and chemical portion of ATC code. Only medications with Reason for Use of Asthma on eCRF will be listed here. Move 'Study Center/Inv' row header to the next page whenever there is not enough room on current page to fit at least one row of data underneath this header.

Listing 4.5 Prior, Concomitant, and Post-Treatment Non-Asthma-Related Medications
Analysis Set: All Subjects Randomized

Add the following footnote: All non-Asthma-related medications taken within 30 days of Screening and while on study are listed.

Listing 4.6 Suspect Drug Assessment for SAEs
Analysis Set: All Subjects Randomized

Subject ID (Treatment Sequence)	SAE Verbatim Term/ Preferred Term/ Onset Date	Additional Non-Study Medication at Onset of SAE	Dose/ Unit/ Route/ Frequency	Started Treatment/ Date of Most Recent Study Treatment/ Blinded or Open/ Treatment at Onset of AE/Non-study drug at onset of SAE	Begin Date/ Stop Date (YYYY-MM-DD)	Con-tin-uing	Duration (Days)	Begin Day/ Stop Day [a]	SAE Causally Related to This Product/Does Principal Investigator feel that SAE may be related to other factor? (Specify)
Center # (Investigator): Center ### (xxxxxxxxxx)									
xxxx (A/B/E/C/D)	Xxxxxxxxxx/ Xxxxxxxxx/ YYYY-MM-DD	Ventolin HFA	90/µg/ IH/PRN	Yes/ YYYY-MM-DD/Blinded or Open-Label/ Yes/Yes	2008-XX-XX	Yes		-22	Yes / Yes (Pre-existing /Underlying disease or Prior or Concomitant Medication
xxxx (B/A/C/E/-)	Xxxxxxxxxx/ Xxxxxxxxx/ YYYY-MM-DD	Atrovent HFA	34/µg/ IH/QID	No	2008-XX-XX/ 2008-XX-XX	No	5	T1_P1/ T1_P5	No

Treatment: A = Placebo, B = AS MDI 90 µg, C = AS MDI 180 µg, D = Proventil 90 µg, E = Proventil 180 µg, - = Not Treated.
XX = Unknown month or day.
[a] A negative number for study day denotes the number of days prior to the start of study treatment. Otherwise, Study Day is Date – Date of dose in the Period + 1. Tx_y = Treatment Period and Day within Treatment Pxx = Days after dose in last Treatment Period.

Sources: xxxxx.sas7bdat
Report generated by program: PT007001/sasdir/programs/statout/l0407.sas Version YYYY-MM-DD xx:xx (Page x of y)

Notes to Programmer: for last column, 2nd question, "Does Principal Investigator feel that SAE may be related to other factor? (Specify)") is only listed on first line for each subject.

4.5 Dosing

Listing 5.1.1 Study Drug Administration
Analysis Set: All Subjects Randomized

Subject ID	Treatment Sequence	Visit (Study Day [a])	Study Drug Administered at Visit	Date and Time of On-Site Study Dose (Study Day [a])	Study Medication Component ID
Study Center # / (Investigator): ### (xxxxxxxxxx)					
xxxxxx	A/E/-/-/-	Visit x (Tx_y)	Yes	YYYY-MM-DD (hh:mm) (Tx_y)	Bxxxxx
		Visit x (Tx_y)	Yes	YYYY-MM-DD (hh:mm) (Tx_y)	Bxxxxx

Treatment: A = Placebo, B = AS MDI 90 µg, C = AS MDI 180 µg, D = Proventil 90 µg, E = Proventil 180 µg, - = Not Treated.
[a] Study Day is Date – Date of dose in the Period + 1. Tx = Period. Tx_y = Period and Day within Period. Pxx=Days after last dose in the last Treatment Period.

Source: xxxxxxx.sas7bdat

Report generated by program: PT007001/sasdir/programs/statout/l050101.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer:
Sort by Center, Subject within Center, Date Dispensed, and Component ID.
Move 'Study Center/Inv' row header to the next page whenever there is not enough room on current page to fit at least one row of data underneath this header.

Listing 5.1.2 Ventolin HFA and Pulmicort Flexhaler Dispensing
Analysis Set: All Subjects Randomized

Subject ID	Treatment Sequence	Drug	Dispensed	Date Dispensed	Study Day [a] of Dispensing	Study Medication Component ID
Study Center # / (Investigator): ### (xxxxxxxxxx)						
xxxxxx	A/E/-/-/-	Ventolin HFA	Yes	YYYY-MM-DD	Tx_y	Axxxxx
		Pulmicort Flexhaler	Yes	YYYY-MM-DD	Tx_y	Axxxxx
		Ventolin HFA	Yes	YYYY-MM-DD	Tx_y	Axxxxx

Treatment: A = Placebo, B = AS MDI 90 µg, C = AS MDI 180 µg, D = Proventil 90 µg, E = Proventil 180 µg, - = Not Treated.
[a] Study Day is Date – Date of dose in the Period + 1. Tx = Period. Tx_y = Period and Day within Period. Pxx = Days after last dose in Period.

Source: xxxxxxx.sas7bdat
Report generated by program: PT007001/sasdir/programs/statout/l050102.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer:
Sort by Center, Subject within Center, Date Dispensed, and Component ID.
Move 'Study Center/Inv' row header to the next page whenever there is not enough room on current page to fit at least one row of data underneath this header.

Listing 5.2 Exposure to Study Treatment
Analysis Set: Safety Analysis Set

Subject ID (Treatment Sequence)	Age (yrs)/ Gender (Race)	Treatment Period	Number of Puffs Taken	Number of Puffs Expected [a]
Center # / (Investigator): ### (xxxxxxxxxx)				
1001	xx/x (xxxx)	1	2	2
(A/B/E/C/D)	xx/x (xxxx)	2	2	x
	xx/x (xxxx)	3	x	x
	xx/x (xxxx)	4	x	x
	xx/x (xxxx)	5	x	x
1002	xx/x (xxxx)	1	1	x
(A/B/E/C/D)	xx/x (xxxx)	2	2	1
	xx/x (xxxx)	3	1	2
	xx/x (xxxx)	4	2	x
	xx/x (xxxx)	5	x	x

Treatment: A = Placebo, B = AS MDI 90 µg, C = AS MDI 180 µg, D = Proventil 90 µg, E = Proventil 180 µg, - = Not Treated.
Race: A=Asian, AIAN=American Indian or Alaska Native, B=Black or African American, NHPI=Native Hawaiian or Other Pacific Islander, O=Other W=White. Gender: F=Female, M=Male.
[a] The expected number of puffs for each treatment day were as follows:

- AS MDI 90 µg (2 actuations of 45 µg/actuation)
- AS MDI 180 µg (2 actuations of 90 µg/actuation)
- Placebo MDI (2 actuations)
- Proventil 90 µg (1 actuation of 90 µg/actuation)
- Proventil 180 µg (2 actuations of 90 µg/actuation)

Source: xxxxxxx.sas7bdat
Report generated by program: PT007001/sasdir/programs/statout/l0502.sas Version YYYY-MM-DD xx:xx
(Page n of N)

Notes to Programmer:
Sort by Center, Subject within Center, and Treatment Period. Move 'Study Center/Inv' row header to the next page whenever there is not enough room on current page to fit at least one row of data underneath this header. Treatment is actual treatment.

4.6 Individual Efficacy Data

4.6.1 Efficacy

Listing 6.1 Subjects Who Failed Restrictions Prior to Spirometry Assessment
Analysis Set: All Subjects Randomized

						Prior to Study Visit, Subject has	
Subject ID	Treatment Sequence	Visit	Study Time Window of Assessment	Effort Date	Effort Time (24 h clock)	Not Had Xanthine Containing Products for at Least 6 Hours	Withheld Asthma Medications Including Corticosteroids for at Least 6 Hours
Center # (Investigator): Center ### (xxxxxxxxxx)							
xxxxxx	A/B/E/C/D	Day 1	Pre-Dose 60 Min	YYYY-MM-DD	8:14:57	No	

Treatment: A = Placebo, B = AS MDI 90 µg, C = AS MDI 180 µg, D = Proventil 90 µg, E = Proventil 180 µg, - = Not Treated.
Note that subjects with missing data for either of the 2 restrictions are also listed.

Source: xxxxxxx.sas7bdat

Report generated by program: PT007001/sasdir/programs/statout/l0601.sas Version YYYY-MM-DD xx:xx (Page n of N

Notes to Programmer:
Sort by Center, Subject ID, and Effort Date.
Only subjects with 'No' or missing responses should be listed.
Move 'Study Center/Inv' row header to the next page whenever there is not enough room on current page to fit at least one row of data underneath this header.

Listing 6.2 Failure of Stability Criteria
Analysis Set: All Subjects Randomized

Subject ID (Treatment Sequence)	Treatment	Visit	(Date of Spirometry Assessment)
Study Center # / (Investigator): ### (xxxxxxxxxx)			
Xxxxxx (A/B/E/C/D)	AS MDI 90 µg	Visit xx	YYYY-MM-DD
		Visit xx	YYYY-MM-DD
Xxxxxx (B/C/-/-/-)	Proventil 180 µg	Visit xx	YYYY-MM-DD

Treatment: A = Placebo, B = AS MDI 90 µg, C = AS MDI 180 µg, D = Proventil 90 µg, E = Proventil 180 µg, - = Not Treated.

Source: xxxxxxx.sas7bdat

Report generated by program: PT007001/sasdir/programs/statout/l0602.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer:
Sort by Center,Subject ID within Center, and Visit.
Move 'Study Center/Inv' row header to the next page whenever there is not enough room on current page to fit at least one row of data underneath this header.

Listing 6.3 Reason for Missed Visit
Analysis Set: All Subjects Randomized

Subject ID (Treatment Sequence)	Treatment	Visit Missed	Missed Due to Asthma Related Issues
Study Center # / (Investigator): ### (xxxxxxxxxx)			
Xxxxxx (A/B/E/C/D)	AS MDI 90 µg	Visit xx	Yes
Xxxxxx (B/C/-/-/-)	Proventil 180 µg	Visit xx	No
		Visit xx	Unknown

Treatment: A = Placebo, B = AS MDI 90 µg, C = AS MDI 180 µg, D = Proventil 90 µg, E = Proventil 180 µg, - = Not Treated.

Source: xxxxxxx.sas7bdat

Report generated by program: PT007001/sasdir/programs/statout/l0603.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer:
Sort by Center, Subject ID within Center, and Visit.
Move 'Study Center/Inv' row header to the next page whenever there is not enough room on current page to fit at least one row of data underneath this header.

Listing 6.4 Spirometry Measurements
Analysis Set: All Subjects Randomized

Subject ID (Treatment Sequence)	Age (yrs)/ Gender/ Race/ Height (cm)	Visit	Treatment/ Treatment Date/Time (24 h clock)	Assessment Date (Study Day) [a]	Rescue Ventolin HFA used? (Time)	Nominal Time of Assessment (Actual Time of Assessment 24 h clock)	Spirometry Assessments Raw Value [Predicted Value at Screening] (Percent of Predicted Value) (grade) [b]						
							FEV_1 (L)	FEV6 (L)	FVC (L)	FEV_1/ FVC(%)	FEF 25-75 (L/sec)	PEFR (L/Min)	PEFT (ms)
Center # (Investigator): Center ### (xxxxxxxxxx)													
Xxxxxx (A/B/E/C/D)	53/F/W/xx x	Visit 1		YYYY-MM-DD (-xx)	NA (xx:xx AM/PM)	60 Min Pre-Dose (xx:xx)	x.xxx [x.xxx] (xx.x%) (x)	x.xxx	x.xxx [x.xxx] (xx.x%) (x)	xx.x	x.xxx [x.xxx] (xx.x%)	xxx.xxx [xxx.xxx] (xx.x%) (x, x)	xxx
		Repeat for Visit 1a, 1b, 2, 3, 4, and 5 and any other visits.	A/ YYYY-MM-DD/ hh:mm	YYYY-MM-DD (Tx_y)	Yes (xxxxxx)	15 Min Post-Dose (xx:xx)	x.xxx (xx.x%) (x)	x.xxx	x.xxx (xx.x%) (x)	xx.x	x.xxx (xx.x%)	xxx.xxx (xx.x%) (x, x)	xxx

Treatment: A = Placebo, B = AS MDI 90 µg, C = AS MDI 180 µg, D = Proventil 90 µg, E = Proventil 180 µg, - = Not Treated.
Race: A=Asian, AIAN=American Indian or Alaska Native, B=Black or African American, NHPI=Native Hawaiian or Other Pacific Islander, O=Other W=White. Gender: F=Female, M=Male.
NA = Not applicable.
[a] Study Day is Date - Date of dose in the Period + 1. Tx = Period. Tx_y = Period and Day within Period. Pxx = Days after dose in last Treatment Period.
[b] Grade is coded: 1=Acceptable 2=Borderline Acceptable 3=Unacceptable.

Source: xxxxxxx.sas7bdat
Report generated by program: PT007001/sasdir/programs/statout/l0604.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer:
Sort by Center,Subject ID, Assessment Date, and Nominal Time of Assessment.
Show Predicted Value only for Screening Visits.
Nominal time of assessment is the SAP-specified derived time window.
Move 'Study Center/Inv' row header to the next page whenever there is not enough room on current page to fit at least one row of data underneath this header.

Listing 6.5 Spirometry Derived Endpoints
Analysis Set: All Subjects Randomized

Subject ID (Treatment Sequence)	Age (yrs)/ Gender/ Race/ Height (cm)	Visit	Assessment Date (Study Day) [a]	Timepoint	Spirometry Derived Endpoints											
					Change from Baseline in FEV_1 AUC_{0-6}	Change from Baseline in FEV_1 AUC_{0-4}	Peak change from baseline in FEV_1 (L)	Change from baseline in FEV_1 (L)	Time to Peak FEV_1 (hours)	Achieved Improvement in FEV_1 from Baseline Within 30 Minutes of Dose		Time to Onset of Response (minutes)		Duration of Response (minutes)	
										12%	15%	12%	15%	12%	15%
Center # (Investigator): Center ### (xxxxxxxxxx)															
Xxxxxx (A/B/E/C/D)	53/F/W/xx x	Visit 2	YYYY-MM-DD (Tx_y)	60 Min Pre-Dose				x.xxx							
		Repeat for Visit 1a, 1b, 2, 3, 4, and 5 and any other visits, and include all pre- and post-dose timepoints.	YYYY-MM-DD (xx)	30 Min Post-Dose	x.xxx	x.xxx	x.xxx	x.xxx	x.xx	Yes	No	x.xx	x.xx	x.xx	x.xx

Treatment: A = Placebo, B = AS MDI 90 µg, C = AS MDI 180 µg, D = Proventil 90 µg, E = Proventil 180 µg, - = Not Treated.
Race: A=Asian, AIAN=American Indian or Alaska Native, B=Black or African American, NHPI=Native Hawaiian or Other Pacific Islander, O=Other W=White. Gender: F=Female, M=Male.
NA = Not applicable.
[a] Study Day is Date – Date of dose in the Period + 1. Tx = Period. Tx_y = Period and Day within Period. Pxx = Days after dose in last Treatment Period.

Source: xxxxxxx.sas7bdat

Report generated by program: PT007001/sasdir/programs/statout/l0605.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer:
Report FEV_1 AUC_{0-6}, FEV_1 AUC_{0-4}, Peak change from baseline in FEV_1, and Time to Peak FEV_1, only at the last timepoint for each treatment period.
Report Achieved 12% Improvement in FEV1 from Baseline Within 30 Minutes of Dose, Achieved 15% Improvement in FEV1 from Baseline Within 30 Minutes of Dose, Time to Onset of Response, and Duration of Response only at 30 minute post-dose timepoint.
Sort by Center,Subject ID, Assessment Date, and Timepoint.
Move 'Study Center/Inv' row header to the next page whenever there is not enough room on current page to fit at least one row of data underneath this header.

4.7 Adverse Event Listings

Listing 7.1 Adverse Events by Primary System Organ Class, Preferred Term, Treatment, Country, Center, Subject ID, and Onset Day
Analysis Set: All Subjects Randomized

Primary System Organ Class: xxxxxxxxxxxxxxxx

Preferred Term	Treatment	Center # (Investigator)	Subject ID (Treatment Sequence)	Age (yrs) /Gender (Race)	Treatment Emergent / Serious AE? [a]	Onset Date (Day) [b] / Occur before or after start of a treatment On Day 1	Duration of Event [c]	Severity / Relationship	Action (Outcome) (AE Treated)	Study Day Resolved /Death [b]
xxxxxxxxxxxxxxx	xxxxxxxxxx xxxxxx	xxxxxxxxx ### (xxxxxxxxxx)	Xxxxxx (A/B/E/C/D)	Xx/F (xxxx)	Yes / No	YYYY-MM-DD (T1_P1)	xx	Moderate / Related	Not Applicable(Recovered/Resolved) (Yes)	T1_P5
				Xx/F (xxxx)	Yes / No	YYYY-MM-DD (T2_P2)	xx	Moderate/ Not Related	Drug Interrupted(Recovering/Resolving)g (Yes)	
	xxxxxxxxxx xxxxxx	xxxxxxxxx ### (xxxxxxxxxx)	Xxxxxx (A/B/E/C/D)	Xx/F (xxxx)	Yes / Yes	YYYY-MM-DD (T1_P1)	xx	xxxxxxxx/ xxxxxxxxx	Dose not changed (Recovered/Resolved with sequelae)(No)	T1_P7
		xxxxxxxx ### (xxxxxxxxxx)	Xxxxxx (A/B/E/C/D)	Xx/F (xxxx)	Yes / No	YYYY-MMDD (T2_P2)	xx	xxxxxxxx/ xxxxxxxxx	Dose not changed (Recovered/Resolved with sequelae)(No)	
…										
xxxxxxxxxxxxxxxxxx xxxx	xxxxxxxxxx xxxxxx	xxxxxxxxxx ### (xxxxxxxxxx)	Xxxxxx (A/B/E/C/D)	Xx/F (xxxx)	# /No	YYYY-MM-DD (T1_P1)	xx	xxxxxxxx/ xxxxxxxxx	Dose not changed (Recovered/Resolved with sequelae)(Yes)	
			Xxxxxx (A/B/E/C/D)	Xx/F (xxxx)	Yes / Yes	YYYY-MM-DD (T2_P2)	xx	xxxxxxxx/ xxxxxxxxx	Drug withdrawn (Recovering/Resolving)	

(Yes)

Treatment: A = Placebo, B = AS MDI 90 µg, C = AS MDI 180 µg, D = Proventil 90 µg, E = Proventil 180 µg, - = Not Treated.
Race: A=Asian, AIAN=American Indian or Alaska Native, B=Black or African American, NHPI=Native Hawaiian or Other Pacific Islander, O=Other W=White. Gender: F=Female, M=Male.
[a] # indicates that it could not be determined whether the AE had onset during study treatment.
[b] A negative number for study day denotes the number of days prior to the start of study treatment. Otherwise, Study Day is Date - Date of dose in the Period + 1. Tx = Period. Tx_y = Period and Day within Period. Pxx = Days after dose in last Treatment Period. On Study Day 1, an @ indicates that event started before study drug administration.
On Study Day 1, @@ indicates that event started after study drug administration.
[c] Duration of Event = Stop Day - Onset Day + 1.

Source: xxxx.sas7bdat

Report generated by program: PT007001/sasdir/programs/statout/l0701.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer:
Sort by Primary System Organ Class, Preferred Term, Actual Treatment, Center, Subject ID within Center, and Onset Day.
Put a blank line after each Center. Present the preferred term, treatment, center (investigator name), Subject ID (Actual Treatment and Age/gender/Race only if start a new value or at the first line of each page.
When a date of onset or date resolved is only partial, put full date in parenthesis under Study Day.
Move 'Study Center/Inv' row header to the next page whenever there is not enough room on current page to fit at least one row of data underneath this header.

Listing 7.2 Glossary of Adverse Event Preferred Terms vs. Investigator's Verbatim

MedDRA Adverse Event Coding Dictionary		
Primary System Organ Class	Preferred Term	Investigator's AE Verbatim
xxxxxxxxxxxxxx	xxxxxxxxxxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
	xxxxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
		xxxxxxxxxxxx
xxxxxx	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxxxxxxx
		xxxxxxxxxx
	xxxxxxxxxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
xxxxxxxxxxxxxx	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxxxxxxxxxx
		xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx

MedDra Version xx.x was used for coding.

Source: xxxxxxx.sas7bdat

Report generated by program: PT007001/sasdir/programs/statout/l0702.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer: Sort by Primary System Organ Class, Preferred Term, and Verbatim Term. List all unique investigators' AE verbatim.

Listing 7.3 Adverse Events by Treatment, Center, Subject ID, and Onset Day
Analysis Set: All Subjects Randomized

Subject ID (Treatment Sequence)	Age (yrs)/ Gender (Race)	Onset Date (Day) [a]/ Occur before or after start of a treatment On Day 1	Primary System Organ Class	AE Verbatim (Preferred Term)	Treat. Emerg. [b]	Event Seriou s	Duration of Event [c]	Severity	Relation -ship	Action	AE Treated ?	Outcome (Death?)	Day Resolved/ Death [a]
Treatment: AS MDI													
Center # (Investigator): Center ### (xxxxxxxxxx)													
xxxxx (A/B/E/C/D)	Xx/F (xxxx)	YYYY-MM-DD (T1_P1)	xxx xxx xxxxx	AE 1 (xxxxxxxxxxxx)	Yes	No		Moderate	Not related	Dose not changed	No	Recoveri ng/Resol ving	
		YYYY-MM-DD (T1_P1)	xxx xxx xxxx	AE 2 (xxxxxxxxxx)	No	No	xx	Moderate	Related	Drug Interrup ted	Yes	Not Recovere d/Not Resolved (Yes)	T1_P3
			…	…									

Treatment: A = Placebo, B = AS MDI 90 µg, C = AS MDI 180 µg, D = Proventil 90 µg, E = Proventil 180 µg, - = Not Treated.
Race: A=Asian, AIAN=American Indian or Alaska Native, B=Black or African American, NHPI=Native Hawaiian or Other Pacific Islander, O=Other W=White. Gender: F=Female, M=Male.
[a] A negative number for study day denotes the number of days prior to the start of study treatment. Otherwise, Study Day is Date – Date of dose in the Period + 1. Tx = Period. Tx_y = Period and Day within Period. Pxx = Days after dose in the last Treatment Period.
On Study Day 1, an @ indicates that event started before study drug administration.
On Study Day 1, @@ indicates that event started after study drug administration.
[b] # indicates that it could not be determined whether the AE had onset during study treatment.
[c] Duration of Event = Stop Day - Onset Day + 1.

Sources: adae.sas7bdat

Report generated by program: PT007001/sasdir/programs/statout/l0703.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer:
Sort by Actual Treatment, Center, Subject ID, Primary System Organ Class, Preferred Term, and Onset Day. Put a blank line after each subject.
Present the preferred term, latest treatment, center (investigator name), Subject ID, and Age/gender/Race when value changes start a new value or at the first line of each page
Move 'Study Center/Inv' row header to the next page whenever there is not enough room on current page to fit at least one row of data underneath this header.
If Ongoing is ticked on CRF, show 'Ongoing' under Study Day Resolved.

4.8 Laboratory Values

Listing 8.1 Laboratory Test Results (Hematology Panel)
Analysis Set: All Subjects Randomized

Subject ID (Treatment Sequence)	Age (yrs)/ Gender (Race)	Visit (Study Day [a])	Collection Date (Study Day) [a]	Nominal Time of Collection (24 hr clock)	Lab Name	Lab Parameter (Unit)	Assay Value	Reference Range Low-High	Flag [b]
Center # (Investigator): Center ### (xxxxxxxxxx)									
xxxxxx (A/B/E/C/D)	Xx/F (xxxx)	Visit 1 (-xx)	YYYY-MM-DD (-xx)	NA (hh:mm)	xxxxxx	xxxxxxxxx	xxx	xxx-xxx	L/H
		Visit 6 (Tx_Py)	YYYY-MM-DD (Tx_Py)	Post-Treamtent Day (hh:mm)	xxxxxx	xxxxxxxxx	xxx	xxx-xxx	L/H

Treatment: A = Placebo, B = AS MDI 90 µg, C = AS MDI 180 µg, D = Proventil 90 µg, E = Proventil 180 µg, - = Not Treated.
Race: A=Asian, AIAN=American Indian or Alaska Native, B=Black or African American, NHPI=Native Hawaiian or Other Pacific Islander, O=Other W=White. Gender: F=Female, M=Male.
NA = Not Applicable.
[a] A negative number for study day denotes the number of days prior to the start of study treatment. Otherwise, Study Day is Date - Date of dose in the Period + 1. Tx = Period. Tx_y = Period and Day within Period. Pxx = Days after dose in last Treatment Period.
[b] N = Normal; L = Low; H = High; Abn. = Abnormal; I=Indeterminate.

Source: adlb.sas7bdat

Report generated by program: PT007001/sasdir/programs/statout/l0801.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer:
Sort by Actual Treatment, Center, Subject ID, Date of Visit, Nominal Time of Collection, and Lab Parameter. Thus, show Screening Visit 1 before Visit 6. Visit 1 will not have a treatment time. .
Move 'Study Center/Inv' row header to the next page whenever there is not enough room on current page to fit at least one row of data underneath this header.

Listing 8.2 Laboratory Test Results (Chemistry Panel and Kidney Function)
Analysis Set: All Subjects Randomized

Listing 8.3 Laboratory Test Comments
Analysis Set: All Subjects Randomized

Subject ID (Treatment Sequence)	Visit (Study Day [a])	Collection Date (Study Day [a])	Nominal Time of Collection (24 h clock)	Lab Name	Lab Group	Lab Parameter (Unit)	Assay Value	Reference Range Low-High	Flag [b]	Result Comments
Center # (Investigator): Center ### (xxxxxxxxxx)										
xxxxxx (A/B/E/C/D)	Visit 6 (Tx_Py)	YYYY-MM-DD (Tx_y)	Post-Treatment Day (hh:mm)	LabCorp	Chemistry	Bicarbonate (mmol/L)	18.000	19-34	L	xxxxxx

Treatment: A = Placebo, B = AS MDI 90 µg, C = AS MDI 180 µg, D = Proventil 90 µg, E = Proventil 180 µg, - = Not Treated.
Race: A=Asian, AIAN=American Indian or Alaska Native, B=Black or African American, NHPI=Native Hawaiian or Other Pacific Islander, O=Other W=White. Gender: F=Female, M=Male.
NA = Not Applicable.
[a] A negative number for study day denotes the number of days prior to the start of study treatment. Otherwise, Study Day is Date – Date of dose in the Period + 1. Tx = Period. Tx_y = Period and Day within Period. Pxx = Days after dose in last Treatment Period.
[b] N = Normal; L = Low; H = High; Abn. = Abnormal; I=Indeterminate.

Source: adlb.sas7bdat

Report generated by program: PT007001/sasdir/programs/statout/l0803.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer:
Sort by Actual Treatment, Center, Subject ID, Date of Visit, Nominal Time of Collection, and Lab Parameter.
Move 'Study Center/Inv' row header to the next page whenever there is not enough room on current page to fit at least one row of data underneath this header.

4.9 Other Clinical Observations and Measurements

Listing 9.1 Vital Signs, Weight, and Height
Analysis Set: All Subjects Randomized

Subject ID (Treatment Sequence)	Age (yrs)/ Gender (Race)	Visit Visit Date (Study Day) [a]	Time of treatment (24 h clock)	Nominal Time of Assessment	Systolic BP (Change from baseline) [b] (mmHg)	Diastolic BP (Change from baseline) [b] (mmHg)	Heart Rate (BPM)	Height (cm)	Weight (kg)	BMI (kg/m^2)
Center # (Investigator): Center ### (xxxxxxxxxx)										
Xxxxxx (A/B/E/C/D)	Xx/F (xxxx)	Screening Visit 1 YYYY-MM-DD (Tx_y)		NA	xxx	xxx	xxx	xxx	xxx.x	xxx.x
	Xx/F (xxxx)	Screening Visit 2 YYYY-MM-DD (Tx_y)		NA	xxx	xxx	xxx	xxx	xxx.x	xxx.x
	Xx/F (xxxx)	Visit x YYYY-MM-DD (Tx_y)	hh:mm	NA	xxx	xxx	xxx	xxx	xxx.x	xxx.x
	Xx/F (xxxx)	Visit x YYYY-MM-DD (Tx_y)	hh:mm	Pre-Dose	xxx	xxx	xxx			
		Unsch. YYYY-MM-DD (Tx_y)	hh:mm		xxx (xx)	xxx (xx)	xxx (xx)			

Treatment: A = Placebo, B = AS MDI 90 µg, C = AS MDI 180 µg, D = Proventil 90 µg, E = Proventil 180 µg, - = Not Treated.
Race: A=Asian, AIAN=American Indian or Alaska Native, B=Black or African American, NHPI=Native Hawaiian or Other Pacific Islander, O=Other W=White. Gender: F=Female, M=Male.
NA = Not Applicable.
[a] A negative number for study day denotes the number of days prior to the start of study treatment. Otherwise, Study Day is Date - Date of dose in the Period + 1. Tx = Period. Tx_y = Period and Day within Period. Pxx = Days after dose in last Treatment Period.
[b] For change from baseline, baseline is defined as the last pre-dose measurement taken prior to dosing on Day 1 of a treatment period.

Source: advs.sas7bdat

Report generated by program: PT007001/sasdir/programs/statout/l0901.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer: Sort by Actual Treatment, Center, Subject ID, Date of Visit, and Nominal Time of Assessment. Nominal time of assessment of Pre-Dose should be provided for all assessments prior to the study drug dose on a day; Post-Dose values are those after the study drug dose was given on a day. If an assessment is not Pre-Dose or Post-Dose, then show 'NA' instead.
Move 'Study Center/Inv' row header to the next page whenever there is not enough room on current page to fit at least one row of data underneath this header.

Listing 9.2 12-Lead Electrocardiogram (ECG)
Analysis Set: All Subjects Randomized

Subject ID (Treatment Sequence)	Age (yrs)/ Gender (Race)	Visit Visit Date (Study Day) [a]	Treatment Time (24 h clock)	Nominal Time of Assessment	Heart Rate (BPM)	Interval Raw Value						Any Clinically Significant Abnormalities on a Study Day? [b]
						RR (ms)	PR (ns)	QRS Axis (degrees)	QRS (ms)	QT (ms)	QTcF (ms)	
Center # (Investigator): Center ### (xxxxxxxxxx)												
xxxxx (A/B/E/C/D)	Xx/F (xxxx)	Visit 1 YYYY-MM-DD (-xx)	NA	NA	xx.x	xxx	xxx	xx	xxx	xxx	xx	No
		Visit 6 YYYY-MM-DD (Tx_1)		Post-Dose	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	Yes
		Unscheduled YYYY-MM-DD (Tx_Py) Etc…	NA	NA	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	No

Treatment: A = Placebo, B = AS MDI 90 µg, C = AS MDI 180 µg, D = Proventil 90 µg, E = Proventil 180 µg, - = Not Treated.
Race: A=Asian, AIAN=American Indian or Alaska Native, B=Black or African American, NHPI=Native Hawaiian or Other Pacific Islander, O=Other W=White. Gender: F=Female, M=Male.
[a] A negative number for study day denotes the number of days prior to the start of study treatment. Otherwise, Study Day is Date – Date of dose in the Period + 1. Tx = Period. Tx_y = Period and Day within Period. Pxx = Days after dose in last Treatment Period.
[b] Abnormalities at Screening Visits and Pre-Dose on Day 1 of Treatment Period 1 were noted on the Medical History CRF; Abnormalities Post-Dose on Day 1 of Treatment Period 1 or afterward were noted on the Adverse Events CRF.

Source: eg.sas7bdat
Report generated by program: PT007001/sasdir/programs/statout/l0902.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer: Sort by Actual Treatment, Center, Subject ID, Date of Visit, and Nominal Time of Assessment. Nominal time of assessment of Pre-Dose should be provided for all assessments prior to the study drug dose on a day; Post-Dose values are those after the study drug dose was given on a day .If an assessment is not Pre-Dose or Post-Dose, then show 'NA' instead.
Move 'Study Center/Inv' row header to the next page whenever there is not enough room on current page to fit at least one row of data underneath this header.

Listing 9.3 Comments
Analysis Set: All Subjects Randomized

Subject ID	Treatment Sequence	Age (yrs)/ Gender (Race)	Visit	Comment Applies To:	Comments
Study Center # / (Investigator): ### (xxxxxxxxxx)					
xxxxx	A/B/E/C/D	Xx/M (xxxx)	Screening Visit 1		xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
			Screening Visit 1a	Subject Eligibility	xxxxxxxxxxx
			Screening Visit 1b	Study Medication	
			Visit 2 Visit 3 …	Adverse Event	
				Vital Signs	
			Premature	12-Lead ECG	
			Discontinuation	Laboratory Results	
			Telephone Follow-up	Spirometry	
			Unscheduled	Visit Scheduling	
				Other: xxxxxxxxxxxxxx	

Treatment: A = Placebo, B = AS MDI 90 µg, C = AS MDI 180 µg, D = Proventil 90 µg, E = Proventil 180 µg, - = Not Treated.
Race: A=Asian, AIAN=American Indian or Alaska Native, B=Black or African American, NHPI=Native Hawaiian or Other Pacific Islander, O=Other W=White. Gender: F=Female, M=Male.

Source: xxxxxxx.sas7bdat
Report generated by program: PT007001/sasdir/programs/statout/l0904.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer:

Sort by Center, Investigator, Subject ID, Visit, Study Day, and category that comment applies to (Subject Eligibility, Study Medication, etc…).
Move 'Study Center/Inv' row header to the next page whenever there is not enough room on current page to fit at least one row of data underneath this header.
Column and text in YELLOW is optional for studies where one or more 'Visits' are not associated with a Study Day.