AstraZeneca

Statistical Analysis Plan

Study Code	D6930C00002(PT007002)
NCT #	NCT03371459
Date	30 MARCH 2018

Albuterol Sulfate Pressurized Inhalation Suspension(PT007) Cumulative Dose Study in Subjects With Mild to Moderate Asthma

STATISTICAL ANALYSIS PLAN

Trial Sponsor:	AstraZeneca AB
Study Number:	D6930C00002 (PT007002)
Study Phase:	II
Product Name:	Albuterol Sulfate Pressurized Inhalation Suspension (AS MDI); PT007
PIND Number:	136213
Indication:	Asthma
Dosage Form/Strength/Dose	• AS MDI 90 µg dosing sequence as o 1 actuation (90 µg) o 1 actuation (90 µg) o 2 actuations (180 µg) o 4 actuations (360 µg) o 8 actuations (720 µg) for a cumulative dose of 1440 µg

Protocol Title: Albuterol Sulfate Pressurized Inhalation Suspension (PT007) Cumulative Dose Study in Subjects With Mild to Moderate Asthma

Date of Issue: 30 Mar 2018

Version 1.0

Signed Agreement on Statistical Analysis Plan

FINAL SIGN-OFF SIGNATURES

Study Biostatistician: [redacted]

Signature Date

Peer Review Biostatistician: [redacted]

Signature Date

Approved by: [redacted]

Approved by: [redacted]

Approved by: [redacted]

Change Log			
Version No.	**Effective Date**	**Reason for the Change/Revision**	**Supersedes**

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse event
AS	Albuterol Sulfate
AS MDI	Albuterol Sulfate Pressurized Inhalation Suspension
ATC	Anatomical Therapeutic Chemical
ATS	American Thoracic Society
AUC	Area under the curve
AUC_{0-6}	Area under the curve from time 0 to 6
AUC_{0-t}	Area under the curve from time 0 to the time of the last measurable plasma concentration
β-hCG	β-human chorionic gonadotropin
BMI	Body mass index
BPM	Beats per minute
C_{15min}	Plasma concentration observed at 15 minutes post each cumulative dose
CI	Confidence interval
C_{max}	Maximum observed plasma concentration
CRF	Case report form
CTCAE	Common Terminology Criteria for Adverse Events
DMP	Data Management Plan
ECG	Electrocardiogram
eCRF	Electronic case report form
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
H_0	Null hypothesis
H_1	Alternative hypothesis
HFA	Hydrofluoroalkane
ICS	Inhaled Corticosteroid
ITT	Intention-to-treat
IUT	Intersection-union test
IWRS	Interactive web response system
LABA	Long-acting β2-agonist
LLOQ	Lower limit of quantification
MDI	Metered dose inhaler
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent-to-treat
ms	Milliseconds

OTC	Over-the-counter
PCS	Potentially clinically significant
PD	Pharmacodynamic
PFT	Pulmonary function test
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 [$QT/(RR^{1/3})$]
RR	Time from electrocardiogram R wave to the next R wave corresponding to electrical systole
SAE	Serious adverse event
SABA	Short-acting β-agonist
SAP	Statistical analysis plan
SD	Standard deviation
SI	International System of Units (Système International d'Unités)
SOC	System organ class
sPDP	Statistical protocol deviation plan
T_{max}	Time to reach C_{max} after the last dose
TOST	Two one-sided test

1. INTRODUCTION

The Sponsor 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 D6930C00002 (PT007002), Version 4.0 (Amendment 3), dated March 15, 2018.

The SAP should be read in conjunction with the study protocol and the electronic Case Report Forms (eCRFs). This version of the SAP has been developed using the final version of the protocol mentioned above and the final version of the Case Report Forms (CRFs; Revision 02) dated January 30, 2018.

All references to doses of AS MDI and 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 assess the efficacy of AS MDI compared to Proventil on lung function after cumulative doses of up to 1440 µg

2.2 Secondary Objective

- To assess the extrapulmonary pharmacodynamic (PD) effects of AS MDI and Proventil after each cumulative dose up to a cumulative dose of 1440 µg

2.3 Safety Objective

- To assess the safety of cumulative doses of AS MDI relative to Proventil

2.4 PK Objective

- To compare the relative systemic bioavailability of AS MDI and Proventil after cumulative doses up to 1440 µg

3. STUDY ENDPOINTS

3.1 Efficacy Assessments

This is a 2-period, crossover study. Each Treatment Period will be 1 day, with a Washout Period of 3 to 7 days between Treatment Periods. The day of study drug 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

- Baseline-adjusted change from baseline in FEV_1 30 minutes after each cumulative dose

3.3 Secondary Efficacy Endpoint

- Baseline-adjusted FEV_1 area under the curve from time 0 to 6 (AUC_{0-6}) after the last cumulative dose

3.4 Extrapulmonary PD Endpoints

- Extrapulmonary PD will be evaluated at 15 minutes after each cumulative dose and 30, 60, 120, 180, 240, 300, and 360 minutes after the last cumulative dose. The change from baseline at each time point, the maximum change from baseline after the last cumulative dose, and the time-weighted average change after the last cumulative dose will be calculated for the following:
  - QT corrected using Fridericia's formula (QTcF) and heart rate (HR)
  - Serum glucose and potassium
  - Diastolic blood pressure (DBP) and systolic blood pressure (SBP)

3.5 Safety Endpoints

The safety endpoints include:

- Adverse Events (AEs)/serious adverse events (SAEs)

3.6 Albuterol PK Endpoints

- Plasma concentration observed at 15 minutes post each cumulative dose (C_{15min})
- AUC from time 0 to the time of the last measurable plasma concentration (AUC_{0-t}) post the final cumulative dose
- Maximum observed plasma concentration (C_{max}) and time to reach C_{max} (T_{max}) after the last dose

4. STUDY DESIGN

4.1 Study Design and Plan

This is a randomized, cumulative dose, open-label, 2-period crossover, multi-center study to assess the safety, efficacy, PK, and extrapulmonary PD of cumulative doses of AS MDI

compared to cumulative doses of Proventil as an active control in subjects with mild to moderate asthma.

This study will be conducted at 5 sites in the US, contributing approximately 8 subjects per site. Across these sites, it is planned that approximately 38 subjects with mild to moderate asthma will be randomized to provide approximately 30 subjects to complete the study. Approximately 20 subjects will also participate in a PK substudy. Pharmacokinetic samples will be collected 15 minutes after each cumulative dose and through 12 hours after the last dose of study drug.

A Study Flow Diagram is displayed in Figure 1.

For more details on the study plan please refer to Protocol Section 4.1.

Inclusion criteria for the study are listed in Section 3.1 of Protocol D6930C00002. Subjects eligible for enrollment in the study must meet all of the inclusion criteria.

Exclusion criteria for the study are listed in Section 3.2 of Protocol D6930C00002. Subjects meeting any of the exclusion criteria are to be excluded from the study.

Randomization criteria for the study are listed in Section 3.3.1 of Protocol D6930C00002.

[redacted]

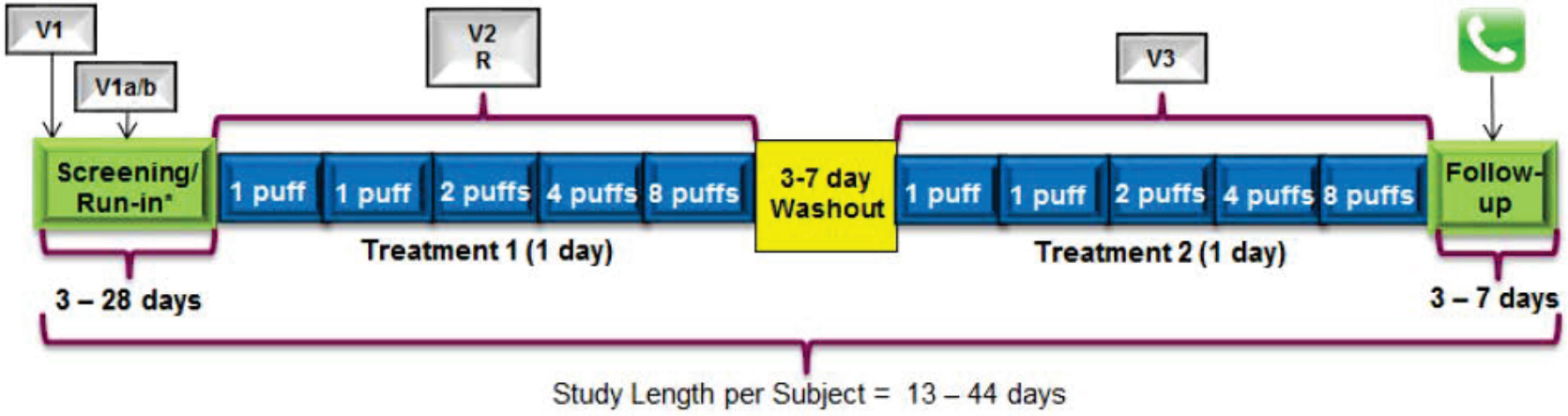
The sequence of visits is displayed in the Study Flow Diagram (Figure 1).

Detailed schedules for pre- and post-dose procedures to be performed on 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 (Visit 2 and Visit 3) are provided in Table 2.

Figure 1 Study Flow Diagram:

Figure 1 Study Design Flow Chart



*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: V=visit; R=randomization.

Table 1 Schedule of Events

	Screening[a]		Treatment Phase			Follow-up
	Visit 1	Visit 1a/1b	Visit 2 Randomization (TP 1)	Visit 3[b] (TP 2)	PDV (if applicable)[c]	TC 3-7 days after final dose
Treatment Day[a]	Day -28 to Day -1		Day 1			
Procedures						
Informed consent	X					
Eligibility criteria	X					
Verify randomization criteria			X			
Verify continued eligibility		X		X		
MDI demonstration/training	X		X	X		
Ventolin reversibility test[d]	X	X				
Medical/surgical history	X					
Demographics	X					
Concomitant medications[e]	X	X	X	X	X	
Spirometry[d]	X	X	X	X		
[redacted]				X		
Physical examination[f]	X			X	X	
SBP/DBP	X		X	X	X	
12-lead ECG	X		X	X	X	
Pregnancy test[g]	X		X			
Clinical laboratory testing	X					
PD sample collection			X	X	X	
Adjust asthma medications per protocol[h]	X			X	X	
Randomization			X			
Randomized study drug administered			X	X		
PK sample collection[i]			X	X		
AEs	X	X	X	X	X	X

Table 1 Schedule of Events (continued)

	Screening[a]		Treatment Phase			Follow-up
	Visit 1	Visit 1a/1b	Visit 2 Randomization (TP 1)	Visit 3[b] (TP 2)	PDV (if applicable)[c]	TC 3-7 days after final dose
Treatment Day[a]	Day -28 to Day -1		Day 1			
Procedures						
Telephone contact						X

Abbreviations: AE=adverse event; DBP=diastolic blood pressure; ECG=electrocardiogram; FEV_1=forced expiratory volume in 1 second; MDI=metered dose inhaler; PDV=Premature Discontinuation Visit; PK=pharmacokinetic; SABA= short-acting β-agonist; SBP=systolic blood pressure; TC=telephone call; TP=Treatment Period.

Note: When post-dose data collection timepoints are concurrent, variables will be collected in the following order: blood pressure, ECG, clinical laboratory assessments, PK blood samples (if applicable), 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 inhaled corticosteroid (ICS) or ICS/long-acting β-agonist (LABA) before study entry.
b Subjects to return to clinic within 3 to 7 days following Treatment Visit 2.
c Subjects who prematurely withdraw from the study will undergo a Premature Discontinuation Visit (see Protocol Section 4.2.4).
d For subjects who received their regularly inhaled asthma medications and/or SABA on the morning of the visit, 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 the time of the last dose of asthma medications. The visit must be rescheduled if the last dose of Ventolin was <48 hours before Visit 2, or if the last dose of Atrovent was <8 hours before Visit 2 or Visit 3.
f Includes evaluation of height and weight at Visit 1.
g A serum pregnancy test (β-human chorionic gonadotropin [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 Protocol Section 7.7.2. At the end of Visit 3 (or upon premature discontinuation, if applicable), subjects will return to pre-study or other appropriate inhaled maintenance asthma medications.
i For subjects in the PK substudy only.

Table 2 Timed Assessments at Each Treatment Visit (Visit 2 and Visit 3)

	Pre-Dose (minutes)		Doses 1 through 4 (minutes)			Dose 5 (minutes)											
	-60	-30	0	15	30	0	15	30	60	120	180	240	300	360	480	600	720
SBP/DBP	X[a]			X			X	X	X	X	X	X	X	X			
12-lead ECG[b]	X[a]			X			X	X	X	X	X	X	X	X			
Sample collection for glucose and potassium	X[a]			X			X	X	X	X	X	X	X	X			
PK sample collection[c]		X		X			X	X	X	X	X	X	X	X	X	X	X
Spirometry	X	X			X[d]		X	X	X	X	X	X	X	X			
Study drug administration			X			X											

Abbreviations: DBP=diastolic blood pressure; ECG=electrocardiogram; PK=pharmacokinetic; SBP=systolic blood pressure.

Note: When post-dose data collection timepoints are concurrent, variables will be collected in the following order: blood pressure, ECG, samples for serum glucose and potassium, PK blood samples (if applicable), and spirometry.

a. Pre-dose assessment to be performed within 60 minutes before the first dose.

b. ECG assessment of QTc interval and heart rate.

c. For subjects in the PK substudy only.

d. The 30-minute spirometry assessment should be started at approximately 25 minutes post-dose to allow for completion of the test before the next dose, so as not to delay dosing.

4.2 Randomization

Subjects will be randomly assigned to 1 of 2 treatment sequences, A/B or B/A, using an interactive web response system (IWRS). Each sequence will comprise the following cumulative dose treatment arms:

• A=AS MDI 1+1+2+4+8 inhalations of 90 µg per inhalation

• B=Proventil 1+1+2+4+8 inhalations of 90 µg per inhalation

Randomization will be centralized.

4.3 Hypothesis Testing

Hypothesis testing for safety will not be performed.

Hypothesis testing for efficacy will be performed within the context of a linear mixed model analysis, including both treatments. For the primary efficacy comparisons for change from baseline in FEV_1 30 minutes post each of the cumulative doses, the primary endpoint, the null hypothesis at each individual time point is that the mean test treatment effect is not equal to that of Proventil; the alternative hypothesis is that the test treatment effect and that of Proventil are equal. Thus, testing will be for equivalence, using a margin of 200 mL and the two, one-sided test (TOST) procedure with alpha = 0.05. In practice, TOST can be implemented by comparing the 90% confidence intervals (CIs) of the between-treatment comparisons for containment within ± 200 mL.

The primary null (H_0) and alternative (H_1) hypotheses with µ representing the mean will be assessed using an intersection-union test (IUT) as follows:

- H_0: $\bigcup_{j=1}^{5} |\mu_{\text{AS MDI}} - \mu_{\text{Proventil}}| > 200$ mL
  that is, following at least 1 of the 5 cumulative doses the difference in treatment means for the change from baseline in FEV_1 30 minutes post doses is not within the limits ± 200 mL
- H_1: $\bigcap_{j=1}^{5} |\mu_{\text{AS MDI}} - \mu_{\text{Proventil}}| \leq 200$ mL
  that is, the difference in treatment means for the change from baseline in FEV_1 30 minutes post all 5 of the cumulative doses are within the limits ± 200 mL

The Type I error rate for the IUT is at most 5% (Berger and Hsu, 1996). Other than the specification of secondary endpoints, no adjustments for Type I error will be made.

4.4 Interim Analysis

No interim analyses are planned for this trial.

4.5 Sample Size

Randomization of 38 subjects to achieve 30 subjects completing the study will provide 95% probability to demonstrate equivalence within ±200 mL after all 5 cumulative doses (IUT). This calculation assumes a true treatment difference (AS MDI–Proventil) of 35 mL, intra-subject standard deviation of 174 mL, and TOST at the 5% level.

Enrollment of 20 subjects to obtain 14 subjects completing the PK substudy will provide 95% probability to observe a one-sided upper 95% confidence bound for the C_{max} ratio (AS MDI/Proventil) that is less than 1.50 even if the true ratio is as high as 1.15. This calculation assumes an intra-subject coefficient of variation of 22% for Proventil and a one-sided 5% test.

5. DATA AND ANALYTICAL QUALITY ASSURANCE

The overall quality assurance (QA) 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 (DMP), Data Validation Check Specifications, and Integrated Safety Data Review Plan. Detailed statistical and programming quality control (QC) and QA procedures are documented in the Statistical Analysis and Programming QC/QA Plan.

Transfer of pulmonary function test (PFT) data from the central PFT laboratory [redacted] will be defined in the [redacted] DMP, 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 [redacted] by qualified personnel. Quality grading assessments will be based on American Thoracic Society (ATS)/European Respiratory Society (ERS) criteria and will be included in data transfers.

6. ANALYSIS SETS

Any evaluability criteria with a potential impact on efficacy, extrapulmonary PD, and PK results will be defined in a statistical protocol deviation plan (sPDP). The evaluability criteria will be programmatically identified in a blinded fashion aided by a review of blinded 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 set or require exclusion of data from a specific timepoint or treatment period and/or subsequent timepoints or a subsequent treatment period for an endpoint(s). Protocol deviations for exclusion of data from the analysis sets will be agreed by the clinical study team and documented in the blinded data review meeting minutes prior to database lock.

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 study drug and receive at least 1 dose of the study drug. Subjects will be analyzed in each period according to

the study drug they were assigned to per the randomization scheme (Note that a subject who used a study drug but took less than 1 full dose of study drug will qualify for this analysis set).

6.2 Modified ITT (mITT) Analysis Set

The Modified ITT (mITT) Analysis Set is a subset of ITT Analysis Set including subjects who received study drug and have post-study drug efficacy data from both Treatment Periods. Data judged to be impacted by major protocol deviations will be determined prior to database lock in a blinded fashion and excluded per the sPDP. Statistical tabulations and analyses will be by randomized study drug, but data obtained after subjects receive an incorrect study drug will be excluded from the affected periods.

6.3 Safety Analysis Set

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

6.4 Per Protocol Analysis Set

The Per Protocol (PP) Analysis Set is a subset of the Safety Analysis Set including subjects who received study drug and have post-study drug extrapulmonary pharmacodynamic data. Data judged to be impacted by major protocol deviations will be determined in a blinded fashion prior to database lock and excluded per the sPDP. Statistical tabulations and analyses will be by randomized study drug, but data obtained after subjects receive an incorrect study drug will be excluded from the affected period(s).

6.5 PK Analysis Set

The PK Analysis Set is defined as subjects in the Safety Analysis Set who received study drug and for whom at least 1 primary PK parameter can be calculated and with no important protocol deviations thought to impact the analysis of the PK data.

6.6 Non-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 (e.g., subjects who were screen failures or stopped participation before being randomized).

6.7 Analysis Sets for Analyses

Analyses will be performed as follows:

Demographics and baseline characteristics will be summarized for the ITT, mITT and Safety Analysis Sets. Extent of exposure will be summarized for the mITT and Safety Analysis Sets. The Safety Analysis Set will be used to summarize AEs and SAEs.

The primary estimand of interest is the De Jure Estimand, defined as the effect of the randomized treatments in all subjects assuming treatments were taken as specified in the protocol. Analysis of

the De Jure Estimand will be conducted as follows: for efficacy (FEV_1-related) endpoints using the mITT Analysis Set; for extrapulmonary PD using the Per Protocol Analysis Set; and for pharmacokinetics using the PK Analysis Set.

The primary endpoint will also be analyzed using the ITT Analysis Set as supportive. Supportive analyses of the extrapulmonary PD parameters will be based on the Safety 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 study drug.

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, safety, extrapulmonary PD, and PK parameters will be summarized by study drug (unless specified otherwise).

7.1.2 Data Exclusion and Missing Data Imputation

Pre-dose spirometry values will use the average of the non-missing -60 min and -30 min values.

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 who received study drug (by randomized study drug and for all subjects), who were withdrawn prematurely, and who completed each study drug.

Length of participation (0 periods, 1 period only, or two periods) will also be tabulated. 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 and a listing of reasons subjects were not randomized will be provided for all subjects not randomized (*Table 1.1.2 and Listing 1.4)*. Reasons for Premature discontinuation will be summarized for the ITT Analysis set by randomized study drug *(Table 1.2.1).* The number and percentage of subjects in the Safety Analysis set withdrawn for each reason will be tabulated by study drug actually received *(Table 1.2.2)*.

The number and percentage of randomized subjects who were included in the ITT, mITT, Safety, PP, and PK Analysis Sets will also be tabulated *(Table 1.1.1)*. The number and percentage of randomized subjects who were in each of the analysis sets will be tabulated for each study drug (i.e., for the set of subjects who were randomized to receive the study drug *[Table 1.3])*.

The reason for exclusion from the mITT Analysis set will be tabulated by study drug for all ITT subjects *(Table 1.4.1)*. The reason for exclusion from the PP Analysis Set will be tabulated by study drug for the Safety set *(Table 1.4.2).* The reason for exclusion from the mITT and PP 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 ITT, Safety, PP, and PK Analysis sets *(Table 1.1.3)*. A listing of subjects who did not comply with use of rescue medication and use of xanthine-containing products (protocol deviations requiring removal of data from the mITT and PP Analysis Set analyses) just prior to spirometry will be provided in *Listing 6.1*. Use of asthma medications 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).* [redacted]

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

7.3 Demography

The demographic variables are age, gender, race, ethnicity, 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 will be summarized for the mITT, ITT, Safety, and PP Analysis Sets and for Non-Randomized subjects *(Tables 1.5.1 through 1.5.5, respectively, and Listing 1.2)*.

7.3.1 Asthma History, Screening 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 medication in the study (Appendix 1) will be summarized for the mITT, ITT, Safety, and PP Analysis Sets *(Tables 1.6.1 through 1.6.4, respectively, and Listing 4.1)*. The screening spirometry variables FEV_1, Forced expiratory flow from 25% to 75% of FVC (FEF_{25-75}), and Forced Vital Capacity (FVC) will be summarized for Visit 1 *(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 data will be derived from Visit 1, 1a, or 1b.

Per Protocol Section 4.1, reversibility to Ventolin HFA (a short-acting β-agonist [SABA]) will be evaluated at Visits 1, 1a (as needed), or 1b (as needed).

Reversibility (i.e. screening reversibility) to Ventolin HFA is defined as having the following condition met at Visit 1, 1a, or Visit 1b:

- Reversibility will be a comparison of the best FEV1 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.

Bronchodilator reversibility to Ventolin HFA 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 and Pregnancy Testing

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

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

Pregnancy Testing Results 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 electronic case report form (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 [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: Q1; March 2018).

Multiple ATC Assignments: If there are multiple ATC codes assigned to the same concomitant medication, the "primary" one based on the Sponsor 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.

Prior Asthma and Non-Asthma Related medications/treatments will be summarized by preferred term and actual study drug received for the Safety Analysis Set separately during the Treatment Periods *(Tables 1.10.1 and 1.10.2, respectively).*

Concomitant Asthma and Non-Asthma Related medications/treatments will be summarized by preferred term and actual study drug received for the Safety Analysis Set separately during the Treatment Periods and the Washout Period between Treatments 1 and 2 *(Tables 1.11.1a, 1.11.1b, 1.11.2a, and 1.11.2b)*. Prior, concomitant, and post-treatment medications will be displayed in separate listings for Asthma and Non-Asthma medications *(Listings 4.4 and 4.5, respectively)*.

Pulmicort Flexhaler and Atrovent dispensing at Visit 2 will be listed *(Listing 5.1.2).*

7.3.4 Extent of Exposure to Study Medication

A listing of study drug dosing information will be provided in Listing 5.1.1. 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. 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

Pre-dose PFT values are known to be variable, and an isolated timepoint may not accurately reflect the true baseline. For this reason, the average of the Visit 2 and Visit 3 pre-dose values will be used as the baseline for analysis. The analysis baseline for the site-collected PFT (pulmonary

function test) parameter FEV_1 will be computed as follows: The mean of the -60 and -30 minute values for each visit day is calculated. Then, the means of the pre-dose values at Visits 2 and 3 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 above in Section 7.4.3.1.

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, unless an actual time is not available; when an actual time is not available, nominal windows will apply to the change from baseline in FEV_1 30 minutes post each of the cumulative doses analyses. Assessments will be allocated to derived nominal collection time windows using the time intervals specified for each below.

Table 3 Analysis Study Time Windows for Spirometry Assessments

Calculated Study Time Window	Time Interval for the Study Time Window
Pre-dose 60 min	≥45 min prior to dose
Pre-dose 30 min	≥0 to <45 min prior to dose
Post-dose 15 min	>0 to 22 min Post-dose
Post-dose 30 min	23 to 44 min Post-dose
Post-dose 1 hr	45 to 89 min Post-dose
Post-dose 2 hrs	90 to 149 min Post-dose
Post-dose 3 hrs	150 to 209 min Post-dose
Post-dose 4 hrs	210 to 269 min Post-dose
Post-dose 5 hrs	270 to 329 min Post-dose
Post-dose 6 hrs	330 to 389 min Post-dose

Note: The time of the study drug dose will be available to the minute. The time of the spirometry assessment will be available to the second, and will be truncated downward to whole minutes prior to calculation of the study time window. Any assessments for which the time interval is 0 due to truncation but are marked as post-dose nominally, will be assigned to the 5 min post dose time window.

For the change from baseline in FEV_1 by timepoint analysis, if there are multiple spirometry values for the same parameter within the same post-dose study time window on the same day, the last value will be chosen for analysis with one exception: if multiples with the exact same time (in minutes and seconds) occur within a window, then the last value based on the nominal time window will be chosen for analysis. Queries to the site (prior to database lock and unblinding) will be used to ascertain which assessment actually occurred first.

7.4.4 Primary Efficacy Analysis

The primary objective of this study is to assess the efficacy of AS MDI compared to Proventil on lung function after cumulative doses of up to 1440 µg.

Change from baseline in FEV_1 30 minutes post each of the cumulative doses will be analyzed using a linear mixed effect model with a random subject effect for the correlation across periods and an unstructured covariance matrix for the repeated measures within subject periods. In the event that the unstructured matrix fails to converge, the heterogeneous Toeplitz will be fit. The fixed effects will include study drug (AS MDI vs Proventil), cumulative dose level, study drug-by-cumulative dose interaction, and period as categorical covariates, and baseline FEV_1 as a continuous covariate. 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 study drug. Ninety-percent (90%) CIs will be calculated for the between-study drug differences after each cumulative dose and will be evaluated for containment within the equivalence bounds of ±200 mL.

The primary analysis will be conducted using the mITT Analysis Set. Supportive analyses will be performed using the ITT Analysis Set. Assumptions underlying the primary analysis will be evaluated and additional analyses may be performed (see Section 7.4.2).

Summary statistics and the results of statistical testing for this analysis will be provided in *Table 2.1.1* with the LS mean change from baseline plotted, in *Figure 2.1.1.1*, for the mITT Analysis. Note that the LS mean values plotted will be obtained from a model using all timepoints assessed during the 8 hours of spirometry testing (the assessments 30 minutes after the first 4 cumulative doses and the assessments through 6 hours after the last cumulative dose), and will use all terms from the primary model.

7.4.5 Secondary Efficacy

7.4.5.1 FEV_1 AUC_{0-6}

The FEV_1 AUC_{0-6} is the area under the curve for change from baseline calculated using the trapezoidal rule and will be normalized by dividing the AUC by the length of follow up post the last cumulative dose (typically 6 hours). The FEV_1 AUC_{0-6} will be calculated if there is at least 1 non-missing data point during the first 2 hours post-dose. 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. 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 study drug, baseline FEV_1, and period. A 90% CI for the between-study drug difference will be calculated and assessed for containment with the equivalence bounds of ±200 mL.

The secondary efficacy analysis will be conducted using the mITT Analysis Set (FEV_1 AUC_{0-6}: *Table 2.2.1)*.

7.4.5.2 Extrapulmonary PD

Extrapulmonary PD parameters of change from baseline at each assessment time, maximum change from baseline post the last cumulative dose, and time-weighted average change from baseline post the last cumulative dose in QTcF, HR, serum glucose, serum potassium, SBP, and DBP will each be analyzed using a similar model as described above for FEV_1 parameters. Period-specific baseline for the relevant parameter will be included as the baseline covariate in the model. Period-specific baseline is defined as the last available pre-dose measurement taken on Day 1 of the treatment period prior to the start of dosing. In addition, a covariate for average baseline (within-subject average across periods) will also be included to remove cross-level bias (Kenward and Roger, 2010). Between-treatment differences and corresponding 90% CIs will be provided.

Summary statistics (n, mean, median, standard deviation, minimum, and maximum) for raw values and change from baseline values in heart rate and QTcF interval will be calculated. These assessments will be tabulated for each study drug for each scheduled pre-dose and post-dose scheduled timepoint of the Treatment Period (change from baseline in QTcF: *Table 2.3.1.1 and Figure 2.3.1.1 and Table 2.3.2.1 and Figure 2.3.2.1 for the PP and Safety Analysis Sets, respectively;* maximum change from baseline in QTcF: *Table 2.3.1.2 and Table 2.3.2.2 for the PP and Safety Analysis Sets, respectively;* time-weighted average change from baseline in QTcF: *Table 2.3.1.3 and Table 2.3.2.3 for the PP and Safety Analysis Sets, respectively; c*hange from baseline in HR: *Table 2.4.1.1 and Figure 2.4.1.1 and Table 2.4.2.1 and Figure 2.4.2.1 for the PP and Safety Analysis Sets, respectively;* maximum change from baseline in HR: *Table 2.4.1.2 and Table 2.4.2.2 for the PP and Safety Analysis Sets, respectively;* time-weighted average change from baseline in HR: *Table 2.4.1.3 and Table 2.4.2.3 for the PP and Safety Analysis Sets respectively*). Time windows for tabulations will be those used for spirometry (See Table 3 in Section 7.4.3.4).

Potentially clinically significant electrocardiogram (ECG) parameter values will be identified based on criteria listed in Table 4.

Table 4 Potentially Clinically Significant (PCS) Criteria for ECG Values, QTcF and Heart Rate

Parameter	Post-Baseline Criteria
QTcF Prolongation	• Post-baseline value is > 450 ms for male subjects or > 470 milliseconds (ms) for female subjects • Post-baseline value is > 500 ms • Increase from baseline is > 30 ms • Increase from baseline is > 60 ms increase • Post-baseline value is > 500 ms and increase > 30 ms • Post-baseline value is > 500 ms and increase > 60 ms
Tachycardia Event	≥ 110 beats per minute (bpm) and increase ≥ 15% from baseline
Bradycardia Event	≤ 50 bpm and decrease ≥ 15% from baseline

Subjects with potentially clinically significant values for QTcF and heart rate ECG values at any time post-baseline during a study visit will be listed by study drug based on the criteria in Table 4 *(Table 2.5.1 and Table 2.5.2 for the Safety Analysis Set for QTcF and Tachycardia/Bradycardia events, respectively)*. All available data for a subject post-baseline including data from unscheduled visits will be presented in the listing.

Summary statistics (n, mean, median, standard deviation, minimum, and maximum) for raw values and change from baseline values in serum glucose and serum potassium will be calculated. These assessments will be tabulated for each study drug for each scheduled pre-dose and post-dose scheduled timepoint of the Treatment Period (change from baseline in serum glucose: *Table 2.6.1.1 and Figure 2.6.1.1 and Table 2.6.2.1 and Figure 2.6.2.1 for the PP and Safety Analysis Sets, respectively;* maximum change from baseline in serum glucose: *Table 2.6.1.2 and Table 2.6.2.2 for the PP and Safety Analysis Sets, respectively;* time-weighted average change from baseline in serum glucose: *Table 2.6.1.3 and Table 2.6.2.3 for the PP and Safety Analysis Sets, respectively;* change from baseline in serum potassium: *Table 2.7.1.1 and Figure 2.7.1.1 and Table 2.7.2.1 and Figure 2.7.2.1 for the PP and Safety Analysis Sets, respectively;* maximum change from baseline in serum potassium: *Table 2.7.1.2 and Table 2.7.2.2 for the PP and Safety Analysis Sets, respectively;* time-weighted average change from baseline in serum potassium: *Table 2.7.1.3 and Table 2.7.2.3 for the PP and Safety Analysis Sets, respectively*).

Potentially Clinically Significant Laboratory Values Above/Below a Clinically Relevant Threshold on-treatment, based on CTCAE (Common Terminology Criteria for Adverse Events) 4.03 and other criteria, will be identified based on the thresholds presented in Table 5.

Table 5 Potentially Clinically Significant (PCS) Laboratory Parameter Criteria

Parameter	Post-Baseline Criteria
Chemistry	
Blood Glucose	<2.2 mmol/L
	>13.9 mmol/L
Serum Potassium	<3.0 mmol/L
	>6.0 mmol/L

ULN denotes upper limit of normal.

*CTCAE 4.03 criteria are based on fasting glucose values. However, subjects were not required to fast prior to obtaining blood glucose values.

Subjects with newly occurring or worsening potentially clinically significant laboratory values of glucose and potassium, above or below a clinically relevant threshold value on-study drug, will be listed *(Tables 2.8 for the Safety Analysis Set)*. Pre-dose laboratory assessments on Day 1 of a Treatment Period (subsequent to a Washout Period and washout treatment) will not be attributed to study drug for the purpose of summarizing clinical significance. All available data for a subject post-baseline including data from unscheduled visits will be presented in the listing.

Summary statistics (n, mean, median, standard deviation, minimum, and maximum) for raw values and change from baseline values in systolic and diastolic blood pressure will be calculated. These assessments will be tabulated for each study drug for each scheduled pre-dose and post-dose scheduled timepoint of the Treatment Period (change from baseline in systolic blood pressure: *Table 2.9.1.1 and Figure 2.9.1.1 and Table 2.9.2.1 and Figure 2.9.2.1 for the PP and Safety Analysis Sets, respectively;* maximum change from baseline in systolic blood pressure: *Table 2.9.1.2 and Table 2.9.2.2 for the PP and Safety Analysis Sets, respectively;* time-weighted average change from baseline in systolic blood pressure: *Table 2.9.1.3 and Table 2.9.2.3 for the PP and Safety Analysis Sets, respectively;* change from baseline in diastolic blood pressure: *Table 2.10.1.1 and Figure 2.10.1.1 and Table 2.10.2.1 and Figure 2.10.2.1 for the PP and Safety Analysis Sets, respectively;* maximum change from baseline in diastolic blood pressure: *Table 2.10.1.2 and Table 2.10.2.2 for the PP and Safety Analysis Sets, respectively;* time-weighted average change from baseline in diastolic blood pressure: *Table 2.10.1.3 and Table 2.10.2.3 for the PP and Safety Analysis Sets, respectively*).

Potentially clinically significant changes in systolic and diastolic blood pressure will be defined based on the following criteria provided by the Sponsor:

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

Parameter (mmHg)	Post-Baseline Criteria
Systolic Blood Pressure, increase	≥180 and increase from baseline ≥20
Systolic Blood Pressure, decrease	≤90 and decrease from baseline ≥20
Diastolic Blood Pressure, increase	≥105 and increase from baseline ≥ 15
Diastolic Blood Pressure, decrease	≤50 and decrease from baseline ≥ 15

Subjects with potentially clinically significant values of SBP and DBP at any time post-baseline during a Study Treatment will be summarized by study drug based on the criteria in Table 6 *(Table 2.11 for the Safety Analysis Set)*. All available data post-baseline including data from unscheduled visits will be used for the vital sign listing.

7.4.1 PK Substudy

Pharmacokinetic sample collection will occur prior to dosing and 15 minutes post-dose following doses 1 through 4. Additional PK samples will be collected following Dose 5 at 15, 30, 60, 120, 180, 240, 300, 360, 480, 600, and 720 minutes post-dose.

Actual sampling time points relative to dosing will be used for PK assessments and analysis where available. It is expected that the actual sampling time will generally be available. In any (likely rare) cases when the actual sampling time was not recorded, the scheduled time may be used.

The concentration-time data reported by the bioanalytical laboratory will be evaluated for inclusion in the PK analysis dataset.

Pharmacokinetic parameters will be estimated for those subjects who are included in the PK Analysis Set and will be estimated by noncompartmental analysis (NCA) using the software Phoenix® WinNonlin® (Certara, US).

From the plasma albuterol concentration-time data, the following PK parameters will be estimated for each subject where possible:

AUC_{0-t} The area under the plasma concentration-time curve from 0 to the time of the last measurable plasma concentration post the final cumulative dose

C_{max} The maximum observed plasma concentration, expressed in concentration units

T_{max} The time to reach C_{max}, expressed in hours

C_{15min} The plasma concentration observed at 15 minutes post each cumulative dose

The AUC_{0-t} will be calculated using the linear up-log down trapezoidal method.

The PK parameters C_{15min}, C_{max}, and T_{max} will be obtained from the observed values.

For the purposes of parameter estimation, plasma concentration values below the lower limit of quantification (LLOQ) will be set to missing in the NCA with the exception of those values reported at pre-dose. Pre-dose concentrations that are below the limit of quantification (BLOQ) will be set to zero for the NCA.

Missing values (e.g., no blood sample collected, no value obtained at analysis) will be treated as missing and excluded from the NCA. If there are ≥2 consecutive missing concentration values, the estimation of PK parameters will be evaluated on a case-by-case basis.

For descriptive statistics of concentration-time data and for the concentration figures, all values below LLOQ will be assigned a value of ½ LLOQ except for pre-dose which will be assigned a value of 0 (no geometric mean will be calculated for pre-dose).

Descriptive statistics for plasma concentrations of albuterol by study drug and nominal timepoint will be summarized using the PK Analysis Set (*Table 2.12.1*). The number of observations, mean (CV%), standard deviation (SD), standard error (SE), median, minimum, maximum, geometric mean, and geometric coefficient of variation will be provided for the plasma concentration data at each respective timepoint with the exception of the pre-dose timepoint for which the geometric mean and geometric CV% will not be calculated.

Plasma concentration data falling outside the following time windows, will be excluded from summaries of individual timepoints but included in a listing: Pre-dose (within 30 minutes prior), 15 minutes (+/- 5 minute) post any of the cumulative doses, and 30 minutes (+/- 5 minutes), 60 minutes (+/-5 minutes), 120 minutes (+/- 15 minutes), 180 minutes (+/- 15 minutes), 240 minutes (+/- 15 minutes), 300 minutes (+/- 15 minutes), 360 minutes (+/- 15 minutes), 480 minutes (+/- 15 minutes), 600 minutes (+/- 15 minutes), and 720 minutes (+/- 15 minutes) post the last cumulative dose.

Individual plasma concentrations by Subject ID, Study drug, and Timepoint will be listed using the Safety Analysis Set (*Listing 6.5*). Actual sample collection times will be detailed in the listing.

The serum concentration-time profiles for mean and individual plasma concentrations of albuterol will be presented for each study drug on the linear/linear scale *(Figures 2.12.1.1 and 2.12.1.1a)* and on the linear/log-linear scale *(Figures 2.12.1.2 and 2.12.1.1b)*. Nominal sampling timepoints relative to administration of the first cumulative dose will be used for all mean plots. Actual sampling timepoints will be used for all individual plots. The PK Analysis Set will be utilized for the mean concentration-time profiles, while the Safety Analysis Set will be utilized for individual concentration-time profiles.

Descriptive statistics for C_{max}, AUC_{0-t}, and T_{max} of albuterol following the last cumulative dose will be summarized by study drug *(Table 2.12.2)*. The number of observations, CV%, SD, median, minimum, maximum, geometric mean, and geometric coefficient of variation will be provided. For T_{max}, only the number of observations, median, minimum, and maximum will be presented.

The PK parameters for each study drug will be listed by subject ID and Treatment Period using the PK Analysis Set (*Listing 6.6*).

Natural log-transformed AUC_{0-t} and C_{max} values for albuterol will each be analyzed with a linear mixed effects model containing fixed effects for study drug and period. Subject will be included as a random effect. Estimated geometric mean ratios with 90% CIs will be provided (*Tables 2.13*).

The C_{15min} values for albuterol after each cumulative dose will be analyzed with a power law model. Natural log-transformed C_{15min} will be regressed onto the natural log transformed cumulative dose levels. The model will include fixed effects for period and study drug (AS MDI vs Proventil), and a random intercept. A test for study drug-by-ln-cumulative dose interaction will be conducted. If found to be non-significant at the 5% level, the interaction term will be dropped from the model, parallel slopes will be assumed, and the relative potency of AS MDI vs Proventil will be assessed (Finney, 1978; *Table 2.14*). If the linear or parallel line assumptions required for the Finney method appear to be violated, then an E_{max} model will be used to estimate relative potency. The bias-corrected and accelerated bootstrap will be used to construct 90% CIs. While not a true assessment of dose proportionality, the proportionality of albuterol C_{15min} after cumulative dose administration (cumulative doses of 90, 180, 360, 720, and 1440 µg) will be assessed using the above power law model with separate slopes. The estimates of the slopes and corresponding 90% confidence intervals will be reported separately for each product (AS MDI vs Proventil). Plots of the ln (concentration) by ln (cumulative dose) will be prepared for the PK parameter for albuterol sulfate (*estimates with individual values plotted will be shown for each study drug, Figure 2.14; the slope with 90% confidence limits will be identified on the figures for each study drug*).

7.4.2 Data Validation and Transformation

In general, the distribution of spirometry measures is well approximated by a normal distribution. Under some circumstances, however (e.g., during an exacerbation unrelated to study drug), 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.

Changes in spirometry measures from baseline and from timepoint to timepoint will be examined graphically before database lock, 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.

Time windows for lab, vital sign, and ECG listings (and Extrapulmonary PD tabulations described in Section 7.4.5.2) will be those used for spirometry (See Table 3 in Section 7.4.3.4).

7.5.1 Adverse Events

Adverse events will be collected and coded using the latest version (20.1 or later) of the Medical Dictionary for Regulatory Activities (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, 21.0, 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 medication 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 the 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 Study Completion/Premature Termination eCRF (including the study drug 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 5-7 days after Visit 3 or a discontinuation visit will not be considered treatment-emergent, but will be listed in adverse event data listings.

Adverse Events Counting Rules per Treatment Period or Washout 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 AEs 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 or Atrovent. 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 study drug received including those occurring during the Washout Period or the final Follow-up 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, study drug, center, subject and onset day will be provided (*Listing 7.1*). Reported adverse events by study drug, center, subject, and onset date will also be provided (*Listing 7.3*).

The listing of adverse events will provide the severity, relationship to study drug, action taken and outcome for each adverse event. Any SAEs reported will be listed (*Table 3.7.1)*. 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 medication 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. For the purpose of determining if a death occurred during a Treatment Period (for *Table 3.1.1*), the end of the Treatment Period will be defined as the date of the last day of the washout period following the Treatment Period, the date of the Discontinuation Visit in the Treatment Period, or if these dates are both missing, the date of the last data collection for the Treatment Period (i.e. date of death).

An overview summary table will be prepared. The table will provide the incidences of subjects, for all subjects and for each study drug, 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 Premature withdrawal, and a report of death *(Table 3.1.1, washout treatment-emergent adverse events excluded).* As a supportive analysis, AEs will be assigned to the last randomized study drug received including those occurring during the Washout Period or the final follow-up period *(Table 3.1.2).*

The incidence of an AE for a study drug will be defined as the number and percent of subjects experiencing an event attributable to that study drug. For each group, the following will be prepared for each study drug, 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 study drug *(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 3.9.1-3.9.2).* There will be a separate table for each study drug.
8. The incidence of treatment-emergent adverse events occurring in at least 2% of subjects in any study drug (*Table 3.2.3*, sorted by descending frequency of events in a preferred term).

7.5.2 Clinical Laboratory Data

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 study drug 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 (e.g.., 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), at Visit 1, and for serum glucose and serum potassium at Visits 2 and 3, will be provided in listings *(Listing 8.1 for central laboratory hematology, Listing 8.2 for central laboratory blood chemistry and kidney function).* 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, [redacted]. 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 study drug. These adverse events will be included in the AE summaries; abnormalities prior to the start of study drug will be noted in medical history and listed.

Vital signs, height, weight, BMI, SBP, and DBP, will be listed *(Listing 9.1)*. The analyses of the SBP and DBP parameters are described in the extrapulmonary PD parameter section.

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 at Visit 1 include heart rate, 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)*.

At all other timepoints, only QTcF and heart rate will be assessed. The analyses of the QTcF and heart rate parameters are described in the extrapulmonary PD parameter section.

7.5.5 Physical Examination

Any physical examination abnormality reported after the start of study drug 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 Versions 1 and 2 of the protocol. Subjects randomized after this amendment have spirometry assessments at 180 and 300 minutes in addition to the timepoints outlined in Versions 1 and 2 of the protocol, while those subjects randomized prior to the amendment will not have the 180 and 300 minutes assessments. [redacted] All subjects will be included in the efficacy analyses irrespective of their spirometry sampling scheme.

The protocol was amended again on 15 March 2018. In this version, Version 4, the Per Protocol analysis set is defined and will serve as the primary analysis set for the extrapulmonary pharmacodynamic parameters. The originally planned Safety analysis set is anti-conservative in a non-inferiority/equivalence testing paradigm. In addition, the specification of maximum change from baseline and time-weighted average change from baseline, both after the last cumulative dose, were added to the analyses of extrapulmonary PD parameters.

Section 8.5.5.3 of the protocol describes analysis of natural log-transformed $AUC_{0\text{-}t}$ and C_{max} values for albuterol post the final cumulative dose. To be consistent with cumulative dose studies of other albuterol products, the calculation of $AUC_{0\text{-}t}$ will be implemented using all available concentration measurements including the C_{15min} values obtained subsequent to each cumulative dose. That is, all available concentration values for a given treatment period will be included in the NCA rather than only those following the final cumulative dose.

9. STATISTICAL SOFTWARE

Data processing, statistical screening, descriptive reporting, and analysis of the efficacy, pharmacokinetic, and safety data will be performed using SAS (Version 9.4 or higher). Version 6.4 of Phoenix® WinNonlin® (Certara, US) will be used for the pharmacokinetic NCA analysis.

10. REFERENCES

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Kenward, MG, Roger, JH. (2010) The use of baseline covariates in cross-over studies. Biostatistics 2010; 11: 1–17.

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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

Category	Description	Data Handling Rules
		earliest. Begin date of Condition will be imputed for all subjects as the 1st of the month.
	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	Within-Period Study Day = Date of assessment/event – date of dose of study drug

Category	Description	Data Handling Rules
	assessment/event study drug	within the respective Treatment Period + 1.
	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 study drug 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 study drug).
	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 +

Category	Description	Data Handling Rules
		1.
	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 study drug is the date of the dose of the study drug (Treatment Day 1 of a study drug)
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	Laboratory, Vital Signs, and ECG 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 change from baseline summaries; it will not apply to maximum change from baseline and AUC summaries. All values will be used for AUC summaries.
Spirometry Assessments	Spirometry assessments	• For the change from baseline in FEV_1 by timepoint analysis, if there are multiple spirometry values for the same parameter within the same post-dose study time window on the same day, the last value will be chosen for analysis with one exception: if multiples with the exact same time (in minutes and seconds) occur within a window, then the last value based on the nominal time window will be chosen for analysis. Queries to the site (prior to database lock and unblinding) will be used to ascertain which assessment

Category	Description	Data Handling Rules
		actually occurred first. • For AUC parameters, all post-baseline assessments in the study time window will be used for calculation of AUC for summaries.
AUC calculation for spirometry endpoints	AUC_{0-6} and AUC_{04}	AUC_{0-6} and AUC_{0-4} will be calculated using the trapezoidal rule and actual time of assessment when available and nominal time of assessment otherwise.
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

Category	Description	Data Handling Rules
		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 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

Category	Description	Data Handling Rules
		year and month, then the AE is considered as treatment emergent. Missing/incomplete (partial) AE start and end dates will not be imputed for data listings.
Exposure (hours)	Exposure (hours) (Study drug Duration)	Exposure is defined as [Time (hr:min) of the last dose of a study drug – time (hr:min) of first dose of a study drug + 1].
Hard Coding	**Hard Coding**	Hard Coding is not allowed during data analysis unless it is agreed to in writing by the Sponsor.
PK analysis	Considerations to be made in the calculation of AUC	The following considerations will be made in the calculation of AUC: • AUC will be calculated by the linear up-log down trapezoidal method. • All values below LLQ will be ignored (set to missing) in the non-compartmental analysis. For the purposes of parameter estimation, plasma concentration values below the lower limit of quantification (LLOQ) will be set to missing in the NCA with the exception of those values reported at pre-dose. Pre-dose concentrations that are below the limit of quantification (BLOQ) will be set to zero for the NCA. • Missing values (e.g., no blood sample collected, no value obtained at analysis) will be treated as missing and excluded from the NCA. If there are ≥2 consecutive missing concentration values, the estimation of PK parameters will be evaluated on a case-by-case basis. • For descriptive statistics and the figures, all values below LLQ will be assigned a value of ½ LLQ except for pre-dose which will be assigned a value of 0 (no geometric mean will be calculated for pre-dose).

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 involving multiple measures per period. Use this code for the primary analysis involving Doses 1-5	***RUN THIS MODEL FOR 30 MIN POST-DOSE TIMEPOINT DATA for the PRIMARY EFFICACY ANALYSIS; to obtain estimates for the plots associated with this analysis, run a second model using all timepoints post-dose;** PROC MIXED PLOTS (ALL) METHOD=REML; CLASS SUBJECT PERIOD TRT DOSE ; MODEL Y = BASE PERIOD TRT DOSE TRT*DOSE / DDFM=KENWARDROGER SOLUTION OUTP=OUT; RANDOM SUBJECT; REPEATED DOSE / TYPE=UN SUBJECT=SUBJECT*PERIOD; LSMEANS TRT TRT*DOSE / PDIFF CL ALPHA=0.10 CORR COV; *to obtain 90% Cis for non-inferiority testing; LSMEANS TRT TRT*DOSE / PDIFF CL ALPHA=0.05 CORR COV; *to obtain 95% Cis for the ls mean change from baseline for each treatment; ODS OUTPUT LSMEANS=MEANS; ODS OUTPUT DIFFS=DIFF; RUN; Where BASE is the baseline value of the endpoint, TRT is the treatment, DOSE is the number (1 to 5) of the dose of the repeated measurement within the period. The non-inclusion of SEQUENCE in the model is in accordance with the SAP text. THE PLOTS (ALL) OPTION FOR PROC MIXED WILL BE USED TO GET PLOTS TO PERFORM MODEL DIAGNOSTICS. Influence statistics will be requested.
Linear Mixed Model analysis for a continuous efficacy endpoint, AUC.	PROC MIXED PLOTS (ALL) METHOD=REML; CLASS SUBJECT PERIOD TRT ; MODEL Y = BASE PERIOD TRT / DDFM=KENWARDROGER SOLUTION UTP=OUT; RANDOM SUBJECT; LSMEANS TRT / PDIFF CL ALPHA=0.10 CORR COV; *to obtain 90% Cis for non-inferiority

Test	Template SAS Code for Modeling (SAS Version 9.4)
	testing; LSMEANS TRT / PDIFF CL ALPHA=0.05 CORR COV; *to obtain 95% Cis for the ls mean change from baseline for each treatment; ODS OUTPUT LSMEANS=MEANS; ODS OUTPUT DIFFS=DIFF; RUN; Where BASE is the baseline value of the endpoint and TRT is the treatment. The non-inclusion of SEQUENCE in the model is in accordance with the SAP text. THE PLOTS (ALL) OPTION FOR PROC MIXED WILL BE USED TO GET PLOTS TO PERFORM MODEL DIAGNOSTICS. Influence statistics will be requested.
Linear Mixed Model analysis for a continuous efficacy endpoint involving multiple measures per period. Use this code for the secondary analyses of the Extrapulmonary PD parameters at 15 minutes post doses 1 to 4 and 30, 60, 120, 180, 240, 300, and 360 minutes after the last cumulative dose (Dose 5).	PROC MIXED PLOTS (ALL) METHOD=REML; CLASS SUBJECT PERIOD TRT DOSETIME; MODEL Y = PERBASE PERIOD TRT AVEBASE DOSETIME TRT*DOSETIME / DDFM=KENWARDROGER SOLUTION OUTP=OUT; RANDOM SUBJECT; REPEATED DOSETIME / TYPE=UN SUBJECT=SUBJECT*PERIOD; LSMEANS TRT TRT*DOSETIME / PDIFF CL ALPHA=0.10 CORR COV; ODS OUTPUT LSMEANS=MEANS; ODS OUTPUT DIFFS=DIFF; RUN; Where BASE is the baseline value of the endpoint, TRT is the treatment, DOSETIME is the number (1 to 4) of the dose and the multiple times after the last cumulative dose (Dose 5) of the repeated measurement within the period. The non-inclusion of SEQUENCE in the model is in accordance with the SAP text. THE PLOTS (ALL) OPTION FOR PROC MIXED WILL BE USED TO

Test	Template SAS Code for Modeling (SAS Version 9.4)
	GET PLOTS TO PERFORM MODEL DIAGNOSTICS. Influence statistics will be requested.

Finney method for relative potency	Finney method for relative potency for C15min;
	
	proc mixed data=<analysis dataset>;
	class usubjid period treatment;
	model laval=period treatment ldose/ddfm=kr solution covb;
	repeated period/type=un subject=usubjid;
	estimate 'a1' int 1 treatment 1 0 period 0 0 0 1 ldose 0; *ASI intercept estimate;
	estimate 'a2' int 1 treatment 0 1 period 0 0 0 1 ldose 0; *Proventil intercept estimate;
	estimate 'b' ldose 1; *common slope (a test for parallelism will be performed before assuming a common slope;
	run;
	*where laval is the natural log of response and ldose is the natural log of cumulative dose level;
	
	If the assumptions of linearity and parallelism do not hold, an Emax model will be used instead of the Finney method, and will use a bias-corrected accelerated bootstrap confidence interval.

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: Albuterol Sulfate Pressurized Inhalation Suspension (PT007) Cumulative Dose Study in Subjects With Mild to Moderate Asthma

D6930C00002 (PT007002)

Trial Sponsor:	AstraZeneca AB
Study Number:	D6930C00002 (PT007002)
Study Phase:	II
Product Name:	Albuterol Sulfate Pressurized Inhalation Suspension (AS MDI); PT007
PIND Number:	136213
Indication:	Asthma
Dosage Form/Strength/Dose	• AS MDI 90 µg ex-actuator dosing sequence as o 1 actuation (90 µg) o 1 actuation (90 µg) o 2 actuations (180 µg) o 4 actuations (360 µg) o 8 actuations (720 µg) for a cumulative dose of 1440 µg

Date of Issue: 30 Mar 2018
Version 1.0

Change Log

Version No.	Effective Date	Reason for the Change/Revision	Supersedes

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 D6930C00002 (PT007002) 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 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 (%)
Randomized [a]	xx (xx.x)
Not Randomized (Non-Randomized Analysis Set) [a] [b]	xx (xx.x)
Not Treated [c]	xx (xx.x)
Treated [c]	xx (xx.x)
Treated with AS MDI	xx (xx.x)
Treated with Proventil	xx (xx.x)
Length of Subject Participation in the Study [c]	
2 Treatment Periods	xx (xx.x)
1 Treatment Period only	xx (xx.x)
0 Treatment Periods	xx (xx.x)
Completed Day 1 of Treatment Period	
2 Treatment Periods	xx (xx.x)
1 Treatment Period only	xx (xx.x)
0 Treatment Periods	xx (xx.x)
Completed Study [c]	xx (xx.x)
Premature Discontinuation [c]	xx (xx.x)
ITT Analysis Set [c] [d]	xx (xx.x)
mITT Analysis Set [c] [e]	xx (xx.x)
Safety Analysis Set [c] [f]	xx (xx.x)
Per Protocol Analysis Set [c][g]	xx (xx.x)
PK Analysis Set [c][h]	xx (xx.x)

[a] % = 100 x n/N, where n=# of subjects in category and N=# of screened subjects.
[b] 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).
[c] % = 100 x n/N, where n=# of treated subjects in category and N=# of subjects treated.
[d] 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).
[e] 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 both Treatment Periods. Data judged to be impacted by major protocol deviations were

determined prior to database lock in a blinded fashion 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.

[f] 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.

[g] The Per Protocol Analysis Set was defined as a subset of the Safety Analysis Set including subjects who received Treatment and have post-treatment extrapulmonary pharmacodynamic data. Data judged to be impacted by major protocol deviations were determined prior to database lock in a blinded fashion and excluded per the statistical protocol deviation plan. Statistical tabulations and analyses were by randomized treatment, but data obtained after subjects receive an incorrect treatment were excluded from the affected periods.

[h] The PK Analysis Set was defined as subjects in the Safety Analysis Set who received study drug and for whom at least 1 primary PK parameter could be calculated and with no important protocol deviations thought to impact the analysis of the PK data.

Report generated by program: PT007002/sasdir/programs/statout/t010101.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer: Completed Day 1 of Treatment Period is defined as attending the visit and having at least one post-dose spirometry assessment at the treatment visit.

Table 1.1.2 Reasons for Subjects Not Randomized
Analysis Set: All Screened 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)
Any Failure of Randomization Criteria	xxx (xx.x)
Criteria #X; XXXXXXXXXXXXXXXXXXXXXXX	xxx (xx.x)

Report generated by program: PT007002/sasdir/programs/statout/t010102.sas Version YYYY-MM-DD xx:xx (Page n of N)

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 and Atrovent from Visit 1 to Visit 2, except for allowable allergy medications defined in Table 7 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), the last dose of Sponsor-provided Ventolin was no later than 48 hours before the study visit, and the last dose of Atrovent was no later than 8 hours before the study visit (if SABA is needed in the morning, the visit must be rescheduled)
4. Pre-bronchodilator FEV1 ≥50% percent predicted normal value
5. Has not used >8 actuations per day (ie, 4 doses of 2 actuations per day) of Sponsor-provided rescue medication (Ventolin and Atrovent) 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, Safety, Per Protocol and PK Analysis Sets
Analysis Set: All Subjects

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 was not randomized
		mITT	All	All	All	Subject did not have post-treatment efficacy data from both Treatment Periods
		Safety	All	All	All	Did not receive at least one dose of the study treatment in the study
		PK	Period 1	300, 360 Minutes	All	Subject did not have at least 1 primary PK parameter that could be calculated
xxxxx	A/B	Safety	All	All	All	Subject did not receive treatment in at least 1 treatment period.
xxxxx	B/-	ITT	All	All	All	Subject was not randomized
		mITT	All	All	All	Subject did not have post-treatment efficacy data from both Treatment Periods
		Safety	All	All	All	Did not receive at least one dose of the study treatment in the study
xxxxx	A/-	mITT	All	All	All	Subject took incorrect study medication
xxxxx	B/A	mITT	Period 2	All	All	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx

Treatment: A = AS MDI, B = Proventil, - = Not Treated.
Subjects may be included in an analysis set as a whole, but have treatment period or timepoint data excluded.

Report generated by program: PT007002/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 Reasons for Premature Treatment Discontinuation
Analysis Set: ITT Analysis Set

	AS MDI (N=xxx)	Proventil (N=xxx)
	n (%)	n (%)
Premature Treatment Discontinuation	xx (xx.x)	xx (xx.x)
Reason for Premature Treatment Discontinuation		
Administrative Reasons	xx (xx.x)	xx (xx.x)
Adverse Event	xx (xx.x)	xx (xx.x)
Lack of Efficacy	xx (xx.x)	xx (xx.x)
Subject Discretion		
Withdrawal of Consent	xx (xx.x)	xx (xx.x)
Asthma	xx (xx.x)	xx (xx.x)
Other	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)
Subject Lost-to-Follow-up	xx (xx.x)	xx (xx.x)
Major Protocol Deviation	xx (xx.x)	xx (xx.x)
Protocol-Specified Discontinuation Criteria	xx (xx.x)	xx (xx.x)
FEV_1 Stability Criteria Sec 5.1.4	xx (xx.x)	xx (xx.x)
Requirement of any Prohibited Medications Listed in Sec 7.7.3	xx (xx.x)	xx (xx.x)
Positive Pregnancy Test	xx (xx.x)	xx (xx.x)
Asthma Worsening Requiring Change in Asthma Treatment Sec 3.9	xx (xx.x)	xx (xx.x)
Treatment Code Broken by Investigator	xx (xx.x)	xx (xx.x)
Other	xx (xx.x)	xx (xx.x)

Note: Reasons specified for Other are listed by subject in Listing 1.2

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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: 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

	AS MDI (N=xxx)	Proventil (N=xxx)
	n (%)	n (%)
Intent-to-treat Analysis Set [a]	xx (xx.x)	xx (xx.x)
mITT Analysis Set [b]	xx (xx.x)	xx (xx.x)
Safety Analysis Set [c]	xx (xx.x)	xx (xx.x)
Per Protocol Analysis Set [d]	xx (xx.x)	xx (xx.x)
PK Analysis Set [e]	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 both Treatment Periods. Data judged to be impacted by major protocol deviations were determined prior to database lock in a blinded fashion 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 Per Protocol Analysis Set was defined as a subset of the Safety analysis set including subjects who received Treatment and have post-treatment extrapulmonary pharmacodynamic data. Data judged to be impacted by major protocol deviations were determined prior to database lock in a blinded fashion and excluded per the statistical protocol deviation plan. Statistical tabulations and analyses were by randomized treatment, but data obtained after subjects receive an incorrect treatment were excluded from the affected periods.
[e] The PK analysis set was defined as subjects in the Safety analysis set who received study drug and for whom at least 1 primary PK parameter could be calculated and with no important protocol deviations thought to impact the analysis of the PK data.

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Table 1.4.1 Reason for Exclusion From the mITT Analysis Set
Analysis Set: ITT Analysis Set

Reason for	AS MDI (N=xxx) n (%)	Proventil (N=xxx) n (%)
Exclusion of a Subject from mITT Analysis Set	xx (xx.x)	xx (xx.x)
<Reason 1>	xx (xx.x)	xx (xx.x)
<Reason 2>	xx (xx.x)	xx (xx.x)
…		
Exclusion of a Treatment Period from mITT Analysis Set	xx (xx.x)	xx (xx.x)
<Reason 1>	xx (xx.x)	xx (xx.x)
<Reason 2>	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 1.4.2 Reason for Exclusion From the Per Protocol Analysis Set
Analysis Set: Safety Analysis Set

Table 1.5.1 Demographics and Baseline Characteristics
Analysis Set: All Subjects

Parameter	All Subjects (N=xxx)
Age (Years)[a]	
n	xxx
Mean	xx.x
SD	xx.x
Median	xx.x
Minimum	xx
Maximum	xx
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)
Prior Asthma Medication	
SABA prn only, n (%)	xxx (xx.x)
ICS, n (%)	xxx (xx.x)
ICS/LABA, n (%)	xxx (xx.x)
Weight (kg)	
n	xxx
Mean	xx.x
SD	xx.x
Median	xx.x

Parameter	All Subjects (N=xxx)
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
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 randomization.

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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 frequency. 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 and renumber subsequent 1.5.x tables if Safety Analysis Set is the same as the ITT Analysis Set.

Table 1.5.4 Demographics and Baseline Characteristics
Analysis Set: Per Protocol Analysis Set

Table 1.5.5 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 drug – Date asthma first diagnosed)/30.475, where the day of asthma diagnosed is assumed to be the 1st of the month.

Table 1.6.2 Duration of Asthma
Analysis Set: ITT Analysis Set

Table 1.6.3 Duration of Asthma
Analysis Set: Safety Analysis Set

Note to Programmer: Remove Table 1.6.3 and renumber subsequent 1.6.x tables if Safety Analysis Set is the same as the ITT Analysis Set.

Table 1.6.4 Duration of Asthma
Analysis Set: Per Protocol Analysis Set

Table 1.7.1 Screening Pre- and Post-Bronchodilator 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

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 at which reversibility was determined.

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Table 1.7.2 Screening Pre- and Post-Bronchodilator 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)
Respiratory	xxx (xx.x)
Asthma	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)
Diabetes	xxx (xx.x)
Type I	xxx (xx.x)
Type II	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)
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 [a]	xxx (xx.x)
Medication 1	xxx (xx.x)
Medication 2	xxx (xx.x)

Preferred term is according to WHODRUG DDE + HD version 1Q2018 (March 2018).
[a] Prior medications taken within 30 days of screening.

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Notes to Programmer: Sort Medications by descending frequency of use in AS MDI.

Table 1.10.2 Prior Medications-Non-Asthma-Related
Analysis Set: Safety Analysis Set

Notes to Programmer: Sort Medications by descending frequency of use across AS MDI. Add a row for "Any Prior Non-Asthma Medication".

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

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

Preferred term is according to WHODRUG DDE + HD version 1Q2018 (March 2018).
See Listing 6.4 for the use of Atrovent as rescue medication.

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Notes to Programmer: Sort Medications by descending frequency of use in AS MDI.

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 Treatment Period 1.
All subjects were allowed to use only sponsor-provided Atrovent for relief of symptoms during a Treatment Period and Pulmicort Flexhaler during the Washout Period.
See Listing 6.4 for the use of Atrovent as rescue medication.

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Table 1.11.2a Concomitant Medications During Treatment Period-Non-Asthma-Related
Analysis Set: Safety Analysis Set

Notes to Programmer: Sort Medications by descending frequency of use in across AS MDI. Add a row for "Any Concomitant Non-Asthma 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 across AS MDI. Add a row for "Any Concomitant Non-Asthma Medication".

2. Efficacy, Extrapulmonary PD, and Pharmacokinetics Summary Tables and Figures

Efficacy Parameters

Primary Efficacy Endpoint

Table 2.1.1 Change from Baseline in FEV_1 (L) 30 Minutes Post Each of the Cumulative Doses
Analysis Set: mITT Analysis Set

			LS Mean Differences Between Treatments
Treatment	Baseline FEV_1	Change From Baseline	Proventil
Dose 1 - 90 µg			
AS MDI			
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)
95% CI		(x.xxx, x.xxx)	
90% CI			(x.xxx, x.xxx)
Proventil			
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)	Not Applicable
95% CI		(x.xxx, x.xxx)	
90% CI			
Repeat rows above for:			
Cumulative Dose- 180 µg			
Cumulative Dose- 360 µg			
Cumulative Dose- 720 µg			
Cumulative Dose- 1440 µg			

Baseline is defined as the mean of evaluable 60 and 30 minute pre-dose values across Visits 2 and 3.
LS Mean = least squares mean from a linear mixed effect model with a random subject effect for the correlation across periods and an unstructured covariance matrix for the repeated measures within subject periods. The fixed effects include treatment (AS MDI vs Proventil), cumulative dose level, treatment-by-cumulative dose interaction, baseline FEV_1, and period.

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Note to Programmer: The model will not include treatment sequence. The baseline summary statistics are based on subjects who had at least one 30 min post-dose data point on a Day 1.

Figure 2.1.1.1 Mean Change From Baseline in FEV_1 ± SE (L) 30 Minutes Post Each of the Cumulative Doses and Over the 6 Hours Following the Last Cumulative Dose
Analysis Set: mITT Analysis Set

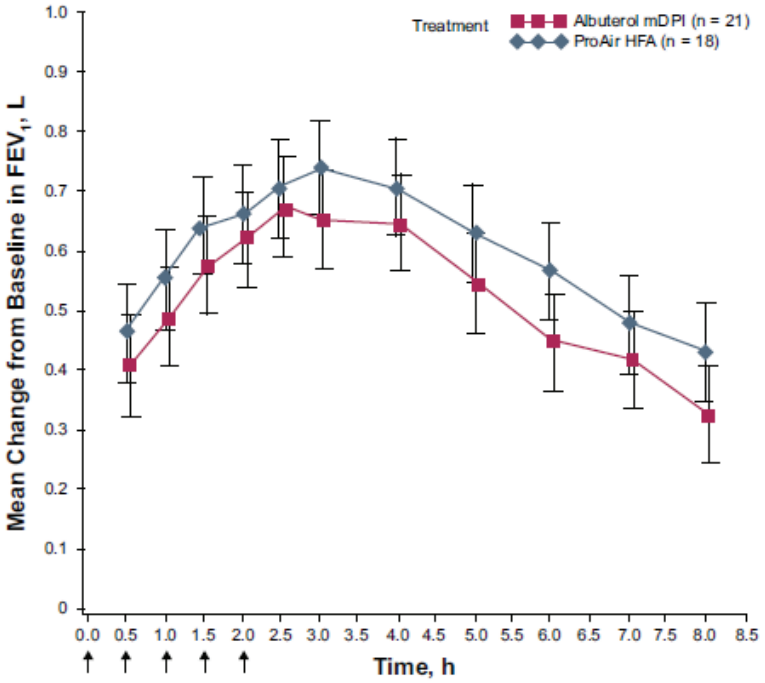

Fig. 2 Least-square mean change from baseline in FEV_1 at each dose and following the cumulative dose in the PP population. *FEV_1* forced expiratory volume in 1 s, *PP* per protocol population. *Bars* indicate standard error of the mean. *Arrows* (↑) indicate dosing times at 0, 0.5, 1, 1.5, and 2 h

Source: Table 2.1.1

Report generated by program: PT007002/sasdir/programs/statout/f02010101.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer: Replace the treatment labels with 'AS MDI' and 'Proventil'.Use actual Cumulative Doses for tick marks instead and values plotted for the x-axis. Use Doses: Dose 1, Dose 2, Dose 3, and Dose 4 and add the assessments through 6 hrs following Dose 5.
Delete the entire caption shown above.

Secondary Efficacy Endpoints

Table 2.2.1 Change from Baseline in FEV_1 AUC_{0-6} (L) After the Last Cumulative Dose
Analysis Set: mITT Analysis Set

Treatment	Baseline FEV_1	Change From Baseline in FEV1 AUC0-6	LS Mean Differences from Proventil
AS MDI			
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)
95% CI		(x.xxx, x.xxx)	
90% CI			(x.xxx, x.xxx)
Proventil			
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)	Not Applicable
95% CI		(x.xxx, x.xxx)	
90% CI			

Baseline is defined as the mean of evaluable 60 and 30 minute pre-dose values across Visits 2 and 3.
LS Mean = least squares mean from a linear mixed effect model with a random subject effect for the correlation across periods. The fixed effects include treatment (AS MDI vs Proventil), cumulative dose level, treatment-by-cumulative dose interaction, baseline FEV_1, and period.

Report generated by program: PT007002/sasdir/programs/statout/t020201.sas Version YYYY-MM-DD hh:mm (Page n of N)

Note to Programmer: The model will not include treatment sequence. The baseline summary statistics are based on subjects who had at least one 30min post-baseline data point on a Day 1.

Extrapulmonary PD

General note to programmers: use the footnotes specified below for Table 2.3.1.1 for all Extrapulmonary PD tables.

Table 2.3.1.1 Change from Baseline in QTcF (ms) 15 Minutes Post Each of the Cumulative Doses and 30, 60, 120, 180, 240, 300, and 360 Minutes After the Last Cumulative Dose
Analysis Set: PP Analysis Set

Notes to Programmer:
Follow the format of Table 2.1.1 and use the following footnote for the extrapulmonary PD model:

Average baseline is defined as the mean of evaluable 60 and 30 minute pre-dose values across Visits 2 and 3.
LS Mean = least squares mean from a linear mixed effect model with a random subject effect for the correlation across periods. The fixed effects include treatment (AS MDI vs Proventil), cumulative dose level, treatment-by-cumulative dose interaction, period-specific baseline FEV_1, average baseline FEV_1, and period.

Figure 2.3.1.1 Adjusted Mean Change From Baseline in QTcF ± SE (ms) 15 Minutes Post Each of the Cumulative Doses and 30, 60, 120, 180, 240, 300, and 360 Minutes After the Last Cumulative Dose
Analysis Set: PP Analysis Set

Notes to Programmer:
Follow the format of Figure 2.1.1.1.
Replace Number of Weeks Post-Dose with Dose and Time. Use Doses and Times: Cumulative Dose 90 µg (15 Min), Cumulative Dose 180 µg (15 Min), Cumulative Dose 360 µg (15 Min), Cumulative Dose 720 µg (15 Min), Cumulative Dose 1440 µg (15 Min), Cumulative Dose 1440 µg (30 Min), Cumulative Dose 1440 µg (60 Min), Cumulative Dose 1440 µg (120 Min), Cumulative Dose 1440 µg (180 Min), Cumulative Dose 1440 µg (240 Min), Cumulative Dose 1440 µg (300 Min), and Cumulative Dose 1440 µg (360 Min).

Table 2.3.1.2 Maximum Change from Baseline in QTcF (ms) Over the 6 Hours Post the Last Cumulative Dose
Analysis Set: PP Analysis Set

Notes to Programmer:
Follow the format of Table 2.1.1.

Table 2.3.1.3 Time-Weighted Average Change from Baseline in QTcF (ms) Over the 6 Hours Post the Last Cumulative Dose
Analysis Set: PP Analysis Set

Notes to Programmer:
Follow the format of Table 2.1.1.

Table 2.3.2.1 Change from Baseline in QTcF (ms) 15 Minutes Post Each of the Cumulative Doses and 30, 60, 120, 180, 240, 300, and 360 Minutes After the Last Cumulative Dose
Analysis Set: Safety Analysis Set

Notes to Programmer:
Follow the format of Table 2.1.1.

Figure 2.3.2.1 Adjusted Mean Change From Baseline in QTcF ± SE (ms) 15 Minutes Post Each of the Cumulative Doses and 30, 60, 120, 180, 240, 300, and 360 Minutes After the Last Cumulative Dose
Analysis Set: Safety Analysis Set

Notes to Programmer:
Follow the format of Figure 2.1.1.1.
Replace Number of Weeks Post-Dose with Dose and Time. Use Doses and Times: Dose 1 (15 Min), Dose 2 (15 Min), Dose 3 (15 Min), Dose 4 (15 Min), Dose 5 (15 Min), Dose 5 (30 Min), Dose 5 (60 Min), Dose 5 (120 Min), Dose 5 (180 Min), Dose 5 (240 Min), Dose 5 (300 Min), and Dose 5 (360 Min).

Table 2.3.2.2 Maximum Change from Baseline in QTcF (ms) Over the 6 Hours Post the Last Cumulative Dose
Analysis Set: Safety Analysis Set

Notes to Programmer:
Follow the format of Table 2.1.1.

Table 2.3.2.3 Time-Weighted Average Change from Baseline in QTcF (ms) Over the 6 Hours Post the Last Cumulative Dose
Analysis Set: Safety Analysis Set

Notes to Programmer:
Follow the format of Table 2.1.1.

Table 2.4.1.1 Change from Baseline in Heart Rate (ms) 15 Minutes Post Each of the Cumulative Doses and 30, 60, 120, 180, 240, 300, and 360 Minutes After the Last Cumulative Dose
Analysis Set: PP Analysis Set

Notes to Programmer:
Follow the format of Table 2.1.1.

Figure 2.4.1.1 Adjusted Mean Change From Baseline in Heart Rate ± SE (ms) 15 Minutes Post Each of the Cumulative Doses and 30, 60, 120, 180, 240, 300, and 360 Minutes After the Last Cumulative Dose
Analysis Set: PP Analysis Set

Notes to Programmer:
Follow the format of Figure 2.1.1.1.
Replace Number of Weeks Post-Dose with Dose and Time. Use Doses and Times: Dose 1 (15 Min), Dose 2 (15 Min), Dose 3 (15 Min), Dose 4 (15 Min), Dose 5 (15 Min), Dose 5 (30 Min), Dose 5 (60 Min), Dose 5 (120 Min), Dose 5 (180 Min), Dose 5 (240 Min), Dose 5 (300 Min), and Dose 5 (360 Min).

Table 2.4.1.2 Maximum Change from Baseline in Heart Rate (bpm) Over the 6 Hours Post the Last Cumulative Dose
Analysis Set: PP Analysis Set

Notes to Programmer:
Follow the format of Table 2.1.1.

Table 2.4.1.3 Time-Weighted Average Change from Baseline in Heart Rate (bpm) Over the 6 Hours Post the Last Cumulative Dose
Analysis Set: PP Analysis Set

Notes to Programmer:
Follow the format of Table 2.1.1.

Table 2.4.2.1 Change from Baseline in Heart Rate (ms) 15 Minutes Post Each of the Cumulative Doses and 30, 60, 120, 180, 240, 300, and 360 Minutes After the Last Cumulative Dose
Analysis Set: Safety Analysis Set

Notes to Programmer:
Follow the format of Table 2.1.1.

Figure 2.4.2.1 Adjusted Mean Change From Baseline in Heart Rate ± SE (ms) 15 Minutes Post Each of the Cumulative Doses and 30, 60, 120, 180, 240, 300, and 360 Minutes After the Last Cumulative Dose
Analysis Set: Safety Analysis Set

Notes to Programmer:
Follow the format of Figure 2.1.1.1.
Replace Number of Weeks Post-Dose with Dose and Time. Use Doses and Times: Dose 1 (15 Min), Dose 2 (15 Min), Dose 3 (15 Min), Dose 4 (15 Min), Dose 5 (15 Min), Dose 5 (30 Min), Dose 5 (60 Min), Dose 5 (120 Min), Dose 5 (180 Min), Dose 5 (240 Min), Dose 5 (300 Min), and Dose 5 (360 Min).

Table 2.4.2.2 Maximum Change from Baseline in Heart Rate (bpm) Over the 6 Hours Post the Last Cumulative Dose
Analysis Set: Safety Analysis Set

Notes to Programmer:
Follow the format of Table 2.1.1.

Table 2.4.2.3 Time-Weighted Average Change from Baseline in Heart Rate (bpm) Over the 6 Hours Post the Last Cumulative Dose
Analysis Set: Safety Analysis Set

Notes to Programmer:
Follow the format of Table 2.1.1.

Table 2.5.1 Listing of ECGs Meeting QTcF Interval Prolongation Criteria
Analysis Set: Safety Analysis Set

Notes to Programmer: Please use Listing 9.2 and add a column after Subject ID identifying which QTcF criteria of the first 6 in the table above is being displayed (criteria shown in Table 3.18.2 above). Put age, gender, and race underneath Subject ID in the first column.

Table 2.5.2 Listing of Potentially Clinically Significant Tachycardia and Bradycardia Events
Analysis Set: Safety Analysis Set

Table 2.6.1.1 Change from Baseline in Serum Glucose (mmol/L) 15 Minutes Post Each of the Cumulative Doses and 30, 60, 120, 180, 240, 300, and 360 Minutes After the Last Cumulative Dose
Analysis Set: PP Analysis Set

Notes to Programmer:
Follow the format of Table 2.1.1.

Figure 2.6.1.1 Adjusted Mean Change From Baseline in Serum Glucose ± SE (mmol/L) 15 Minutes Post Each of the Cumulative Doses and 30, 60, 120, 180, 240, 300, and 360 Minutes After the Last Cumulative Dose
Analysis Set: PP Analysis Set

Notes to Programmer:
Follow the format of Figure 2.1.1.1.
Replace Number of Weeks Post-Dose with Dose and Time. Use Doses and Times: Dose 1 (15 Min), Dose 2 (15 Min), Dose 3 (15 Min), Dose 4 (15 Min), Dose 5 (15 Min), Dose 5 (30 Min), Dose 5 (60 Min), Dose 5 (120 Min), Dose 5 (180 Min), Dose 5 (240 Min), Dose 5 (300 Min), and Dose 5 (360 Min).

Table 2.6.1.2 Maximum Change from Baseline in Serum Glucose (mmol/L) 15 Minutes Post Each of the Cumulative Doses and 30, 60, 120, 180, 240, 300, and 360 Minutes After the Last Cumulative Dose
Analysis Set: PP Analysis Set

Table 2.6.1.3 Time-Weighted Average Change from Baseline in Serum Glucose (mmol/L) 15 Minutes Post Each of the Cumulative Doses and 30, 60, 120, 180, 240, 300, and 360 Minutes After the Last Cumulative Dose
Analysis Set: PP Analysis Set

Table 2.6.2.1 Change from Baseline in Serum Glucose (mmol/L) 15 Minutes Post Each of the Cumulative Doses and 30, 60, 120, 180, 240, 300, and 360 Minutes After the Last Cumulative Dose
Analysis Set: Safety Analysis Set

Notes to Programmer:
Follow the format of Table 2.1.1.

Figure 2.6.2.1 Adjusted Mean Change From Baseline in Serum Glucose ± SE (mmol/L) 15 Minutes Post Each of the Cumulative Doses and 30, 60, 120, 180, 240, 300, and 360 Minutes After the Last Cumulative Dose
Analysis Set: Safety Analysis Set

Notes to Programmer:
Follow the format of Figure 2.1.1.1.
Replace Number of Weeks Post-Dose with Dose and Time. Use Doses and Times: Dose 1 (15 Min), Dose 2 (15 Min), Dose 3 (15 Min), Dose 4 (15 Min), Dose 5 (15 Min), Dose 5 (30 Min), Dose 5 (60 Min), Dose 5 (120 Min), Dose 5 (180 Min), Dose 5 (240 Min), Dose 5 (300 Min), and Dose 5 (360 Min).

Table 2.6.2.2 Maximum Change from Baseline in Serum Glucose (mmol/L) 15 Minutes Post Each of the Cumulative Doses and 30, 60, 120, 180, 240, 300, and 360 Minutes After the Last Cumulative Dose
Analysis Set: Safety Analysis Set

Table 2.6.2.3 Time-Weighted Average Change from Baseline in Serum Glucose (mmol/L) 15 Minutes Post Each of the Cumulative Doses and 30, 60, 120, 180, 240, 300, and 360 Minutes After the Last Cumulative Dose
Analysis Set: Safety Analysis Set

Table 2.7.1.1 Change from Baseline in Serum Potassium (mmol/L) 15 Minutes Post Each of the Cumulative Doses and 30, 60, 120, 180, 240, 300, and 360 Minutes After the Last Cumulative Dose
Analysis Set: PP Analysis Set

Notes to Programmer:
Follow the format of Table 2.1.1.

Figure 2.7.1.1 Adjusted Mean Change From Baseline in Serum Potassium ± SE (mmol/L) 15 Minutes Post Each of the Cumulative Doses and 30, 60, 120, 180, 240, 300, and 360 Minutes After the Last Cumulative Dose
Analysis Set: PP Analysis Set

Notes to Programmer:
Follow the format of Figure 2.1.1.1.

Replace Number of Weeks Post-Dose with Dose and Time. Use Doses and Times: Dose 1 (15 Min), Dose 2 (15 Min), Dose 3 (15 Min), Dose 4 (15 Min), Dose 5 (15 Min), Dose 5 (30 Min), Dose 5 (60 Min), Dose 5 (120 Min), Dose 5 (180 Min), Dose 5 (240 Min), Dose 5 (300 Min), and Dose 5 (360 Min).

Table 2.7.1.2 Maximum Change from Baseline in Serum Potassium (mmol/L) 15 Minutes Post Each of the Cumulative Doses and 30, 60, 120, 180, 240, 300, and 360 Minutes After the Last Cumulative Dose
Analysis Set: PP Analysis Set

Table 2.7.1.3 Time-Weighted Average Change from Baseline in Serum Potassium (mmol/L) 15 Minutes Post Each of the Cumulative Doses and 30, 60, 120, 180, 240, 300, and 360 Minutes After the Last Cumulative Dose
Analysis Set: PP Analysis Set

Table 2.7.2.1 Change from Baseline in Serum Potassium (mmol/L) 15 Minutes Post Each of the Cumulative Doses and 30, 60, 120, 180, 240, 300, and 360 Minutes After the Last Cumulative Dose
Analysis Set: Safety Analysis Set

Notes to Programmer:
Follow the format of Table 2.1.1.

Figure 2.7.2.1 Adjusted Mean Change From Baseline in Serum Potassium ± SE (mmol/L) 15 Minutes Post Each of the Cumulative Doses and 30, 60, 120, 180, 240, 300, and 360 Minutes After the Last Cumulative Dose
Analysis Set: Safety Analysis Set

Notes to Programmer:
Follow the format of Figure 2.1.1.1.
Replace Number of Weeks Post-Dose with Dose and Time. Use Doses and Times: Dose 1 (15 Min), Dose 2 (15 Min), Dose 3 (15 Min), Dose 4 (15 Min), Dose 5 (15 Min), Dose 5 (30 Min), Dose 5 (60 Min), Dose 5 (120 Min), Dose 5 (180 Min), Dose 5 (240 Min), Dose 5 (300 Min), and Dose 5 (360 Min).

Table 2.7.2.2 Maximum Change from Baseline in Serum Potassium (mmol/L) 15 Minutes Post Each of the Cumulative Doses and 30, 60, 120, 180, 240, 300, and 360 Minutes After the Last Cumulative Dose
Analysis Set: Safety Analysis Set

Table 2.7.2.3 Time-Weighted Average Change from Baseline in Serum Potassium (mmol/L) 15 Minutes Post Each of the Cumulative Doses and 30, 60, 120, 180, 240, 300, and 360 Minutes After the Last Cumulative Dose
Analysis Set: Safety Analysis Set

Table 2.8 Listing of All Records for Subjects With Newly Occurring or Worsening Potentially Clinically Significant Serum Glucose and Serum Potassium Laboratory Values Post-Baseline
Analysis Set: Safety Analysis Set

Notes to Programmer: Please use the format of Listing 8.1 and add a column after Subject ID identifying which criterion in Table 3.16.7 is used for the PCS value. Put age, gender, and race underneath Subject ID in the first column. List all records for a subject, not just those meeting the criteria.

Table 2.9.1.1 Change from Baseline in Systolic Blood Pressure (mmHg) 15 Minutes Post Each of the Cumulative Doses and 30, 60, 120, 180, 240, 300, and 360 Minutes After the Last Cumulative Dose
Analysis Set: PP Analysis Set

Notes to Programmer:
Follow the format of Table 2.1.1.

Figure 2.9.1.1 Adjusted Mean Change From Baseline in Systolic Blood Pressure ± SE (mmHg) 15 Minutes Post Each of the Cumulative Doses and 30, 60, 120, 180, 240, 300, and 360 Minutes After the Last Cumulative Dose
Analysis Set: PP Analysis Set

Notes to Programmer:
Follow the format of Figure 2.1.1.1.
Replace Number of Weeks Post-Dose with Dose and Time. Use Doses and Times: Dose 1 (15 Min), Dose 2 (15 Min), Dose 3 (15 Min), Dose 4 (15 Min), Dose 5 (15 Min), Dose 5 (30 Min), Dose 5 (60 Min), Dose 5 (120 Min), Dose 5 (180 Min), Dose 5 (240 Min), Dose 5 (300 Min), and Dose 5 (360 Min).

Table 2.9.1.2 Maximum Change from Baseline in Systolic Blood Pressure (mmHg) 15 Minutes Post Each of the Cumulative Doses and 30, 60, 120, 180, 240, 300, and 360 Minutes After the Last Cumulative Dose
Analysis Set: PP Analysis Set

Table 2.9.1.3 Time-Weighted Average Change from Baseline in Systolic Blood Pressure (mmHg) 15 Minutes Post Each of the Cumulative Doses and 30, 60, 120, 180, 240, 300, and 360 Minutes After the Last Cumulative Dose
Analysis Set: PP Analysis Set

Table 2.9.2.1 Change from Baseline in Systolic Blood Pressure (mmHg) 15 Minutes Post Each of the Cumulative Doses and 30, 60, 120, 180, 240, 300, and 360 Minutes After the Last Cumulative Dose
Analysis Set: Safety Analysis Set

Notes to Programmer:
Follow the format of Table 2.1.1.

Figure 2.9.2.1 Adjusted Mean Change From Baseline in Systolic Blood Pressure ± SE (mmHg) 15 Minutes Post Each of the Cumulative Doses and 30, 60, 120, 180, 240, 300, and 360 Minutes After the Last Cumulative Dose
Analysis Set: Safety Analysis Set

Notes to Programmer:
Follow the format of Figure 2.1.1.1.
Replace Number of Weeks Post-Dose with Dose and Time. Use Doses and Times: Dose 1 (15 Min), Dose 2 (15 Min), Dose 3 (15 Min), Dose 4 (15 Min), Dose 5 (15 Min), Dose 5 (30 Min), Dose 5 (60 Min), Dose 5 (120 Min), Dose 5 (180 Min), Dose 5 (240 Min), Dose 5 (300 Min), and Dose 5 (360 Min).

Table 2.9.2.2 Maximum Change from Baseline in Systolic Blood Pressure (mmHg) 15 Minutes Post Each of the Cumulative Doses and 30, 60, 120, 180, 240, 300, and 360 Minutes After the Last Cumulative Dose
Analysis Set: Safety Analysis Set

Table 2.9.2.3 Time-Weighted Average Change from Baseline in Systolic Blood Pressure (mmHg) 15 Minutes Post Each of the Cumulative Doses and 30, 60, 120, 180, 240, 300, and 360 Minutes After the Last Cumulative Dose
Analysis Set: Safety Analysis Set

Table 2.10.1.1 Change from Baseline in Diastolic Blood Pressure (mmHg) 15 Minutes Post Each of the Cumulative Doses and 30, 60, 120, 180, 240, 300, and 360 Minutes After the Last Cumulative Dose
Analysis Set: PP Analysis Set

Notes to Programmer:
Follow the format of Table 2.1.1.

Figure 2.10.1.1 Adjusted Mean Change From Baseline in Diastolic Blood Pressure ± SE (mmHg) 15 Minutes Post Each of the Cumulative Doses and 30, 60, 120, 180, 240, 300, and 360 Minutes After the Last Cumulative Dose
Analysis Set: PP Analysis Set

Notes to Programmer:
Follow the format of Figure 2.1.1.1.
Replace Number of Weeks Post-Dose with Dose and Time. Use Doses and Times: Dose 1 (15 Min), Dose 2 (15 Min), Dose 3 (15 Min), Dose 4 (15 Min), Dose 5 (15 Min), Dose 5 (30 Min), Dose 5 (60 Min), Dose 5 (120 Min), Dose 5 (180 Min), Dose 5 (240 Min), Dose 5 (300 Min), and Dose 5 (360 Min).

Table 2.10.1.2 Maximum Change from Baseline in Diastolic Blood Pressure (mmHg) 15 Minutes Post Each of the Cumulative Doses and 30, 60, 120, 180, 240, 300, and 360 Minutes After the Last Cumulative Dose
Analysis Set: PP Analysis Set

Table 2.10.1.3 Time-Weighted Average Change from Baseline in Diastolic Blood Pressure (mmHg) 15 Minutes Post Each of the Cumulative Doses and 30, 60, 120, 180, 240, 300, and 360 Minutes After the Last Cumulative Dose
Analysis Set: PP Analysis Set

Table 2.10.2.1 Change from Baseline in Diastolic Blood Pressure (mmHg) 15 Minutes Post Each of the Cumulative Doses and 30, 60, 120, 180, 240, 300, and 360 Minutes After the Last Cumulative Dose
Analysis Set: Safety Analysis Set

Notes to Programmer:
Follow the format of Table 2.1.1.

Figure 2.10.2.1 Adjusted Mean Change From Baseline in Diastolic Blood Pressure ± SE (mmHg) 15 Minutes Post Each of the Cumulative Doses and 30, 60, 120, 180, 240, 300, and 360 Minutes After the Last Cumulative Dose
Analysis Set: Safety Analysis Set

Notes to Programmer:
Follow the format of Figure 2.1.1.1.
Replace Number of Weeks Post-Dose with Dose and Time. Use Doses and Times: Dose 1 (15 Min), Dose 2 (15 Min), Dose 3 (15 Min), Dose 4 (15 Min), Dose 5 (15 Min), Dose 5 (30 Min), Dose 5 (60 Min), Dose 5 (120 Min), Dose 5 (180 Min), Dose 5 (240 Min), Dose 5 (300 Min), and Dose 5 (360 Min).

Table 2.10.2.2 Maximum Change from Baseline in Diastolic Blood Pressure (mmHg) 15 Minutes Post Each of the Cumulative Doses and 30, 60, 120, 180, 240, 300, and 360 Minutes After the Last Cumulative Dose
Analysis Set: Safety Analysis Set

Table 2.10.2.3 Time-Weighted Average Change from Baseline in Diastolic Blood Pressure (mmHg) 15 Minutes Post Each of the Cumulative Doses and 30, 60, 120, 180, 240, 300, and 360 Minutes After the Last Cumulative Dose
Analysis Set: Safety Analysis Set

Table 2.11 Listing of Potentially Clinically Significant Systolic and Diastolic Blood Pressure (mmHg) Increases and Decreases
Analysis Set: Safety Analysis Set

Notes to Programmer: Please use the format of Listing 9.1 and add 2 columns after Subject ID identifying which criteria in the table above are being displayed for a subject (criteria also shown in Table 3.17.2). Put age, gender, and race underneath Subject ID in the first column. In the last column display Visit 1 Height, Weight, and BMI.

Pharmacokinetic Analyses

Table 2.12.1 Descriptive Statistics for Plasma Concentrations of Albuterol (pg/mL) by Treatment and Timepoint
Analysis Set: PK Analysis Set

	Treatment	
Timepoint	AS MDI (N=xxx)	Proventil (N=xxx)
Pre-dose		
N	xx	xx
Mean (CV %)	xx.x (xx.x)	xx.x (xx.x)
SD	xx.xx	xx.xx
SE	xx.xx	xx.xx
Median	xx.x	xx.x
Minimum, Maximum	xx.xx	xx.xx
Geometric Mean (CV %)	xx.x (xx.x)	xx.x (xx.x)
C_{15min}- 90 µg		
N	xx	xx
Mean (CV %)	xx.x (xx.x)	xx.x (xx.x)
SD	xx.xx	xx.xx
SE	xx.xx	xx.xx
Median	xx.x	xx.x
Minimum, Maximum	xx.xx	xx.xx
Geometric Mean (CV %)	xx.x (xx.x)	xx.x (xx.x)

CV % = coefficient of variation in percentage.
With the exception of Day 1 pre-dose values, values below Lower Limit of Quantification (LLQ) are set to LLQ/2 for all descriptive statistics categories. Below LLQ values from Day 1 pre-dose will be set to zero.
Albuterol LLQ = 50 pg/mL

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Notes to Programmer:
C_{15min}- 180 µg, C_{15min}- 360 µg, C_{15min}- 720 µg, C_{15min}- 1440 µg, Cumulative Dose- 1440 µg (30 min post dose), Cumulative Dose- 1440 µg (60 min post dose), Cumulative Dose- 1440 µg (120 min post dose), Cumulative Dose- 1440 µg (180 min post dose), Cumulative Dose- 1440 µg (240 min post dose), Cumulative Dose- 1440 µg (300 min post dose), Cumulative Dose- 1440 µg (360 min post dose), Cumulative Dose- 1440 µg (480 min post dose), Cumulative Dose- 1440 µg (600 min post dose), Cumulative Dose- 1440 µg (720 min post dose).

Figure 2.12.1.1 Mean (+/- SE) Plasma Albuterol Concentration-Time Profile (Linear-Linear Scale)
Analysis Set: PK Analysis Set
Figure 2.12.1.1<a> Individual (+/- SE) Plasma Albuterol Concentration-Time Profile (Linear-Linear Scale)
Analysis Set: Safety Analysis Set

Figure 2.12.1.2<b> Individual (+/- SE) Plasma Albuterol Concentration-Time Profile (Linear/Log-Linear Scale)
Analysis Set: Safety Analysis Set

Figure 2.12.1.2 Mean (+/- SE) Plasma Albuterol Concentration-Time Profile (Linear/Log-Linear Scale)
Analysis Set: PK Analysis Set

Table 2.12.2 Descriptive Statistics for Pharmacokinetic Parameters of Albuterol by Treatment
Analysis Set: PK Analysis Set

Pharmacokinetic Parameter	Treatment	
	AS MDI (N=xx)	Proventil (N=xx)
C_{max} (pg/mL)		
n	xx	xx
Mean (CV%)	xx.x (xx.x)	xx.x (xx.x)
SD	xx.xx	xx.xx
Median	xx.x	xx.x
Minimum; Maximum	xx;xx	xx;xx
Geometric Mean (CV%)	xx.x (xx.x)	xx.x (xx.x)
AUC_{0-t} (pg*hr/mL)		
n	xx	xx
Mean (CV%)	xx.x (xx.x)	xx.x (xx.x)
SD	xx.xx	xx.xx
Median	xx.x	xx.x
Minimum; Maximum	xx;xx	xx;xx
t_{max} (hr)		
n	xx	xx
Median	xx.x	xx.x
Minimum; Maximum	xx;xx	xx;xx

CV % = coefficient of variation in percentage.
With the exception of Day 1 pre-dose values, values below Lower Limit of Quantification (LLQ) are set to LLQ/2 for all descriptive statistics categories.
Albuterol LLQ = 50 pg/mL

Source: Listing 6.6

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Table 2.13 Relative Bioavailability of Albuterol After the Last Cumulative Dose
Analysis Set: PK Analysis Set

	Treatment	Geometric Ls Mean	Geometric Mean Ratio (%) 90% Confidence Interval[a]	Intra-Subject CV%[b]
C_{max} (pg/mL)	AS MDI (n=xx)	xxx.xx	xxx.xx (xxx.xx, xxx.xx)	xxx.xx%
	Proventil (n=xx)	xxx.xx		
AUC_{0-t} (pg*hr/mL)	AS MDI (n=xx)	xxx.xx	xxx.xx (xxx.xx, xxx.xx)	xxx.xx%
	Proventil (n=xx)	xxx.xx		

[a] Ratio (expressed as a percentage) of exponentiated mean difference of ln-transformed PK parameters. The confidence interval is from a linear mixed effect model with a random subject effect and fixed effects for treatment and period.
[b] 100*sqrt[exp(residual) - 1] where residual = the residual variance component.

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Note to Programmer: The model will not include treatment sequence.

Table 2.14 Relative Potency of Albuterol for AS MDI versus Proventil: Finney
Analysis Set: PK Analysis Set

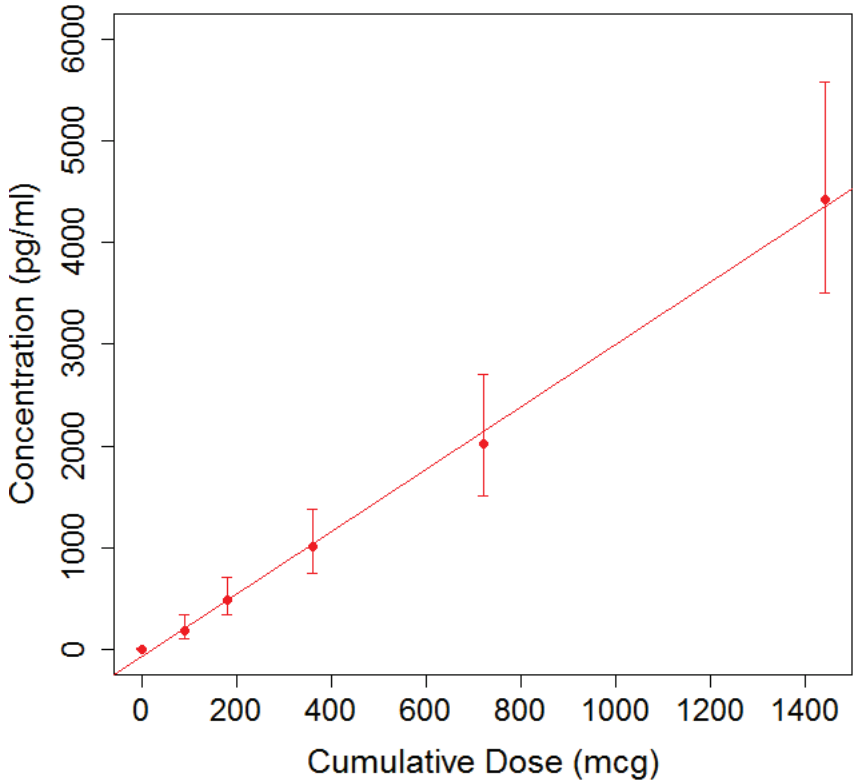
Pharmacokinetic Parameter	Intercept Estimate		Common Slope Estimate	Relative Potency [a]	90% Confidence Interval [a]
	AS MDI (a1)	Proventil MDI (a2)			
C_{15min} (pg/mL)	2.308	2.208	0.875	0.892	0.831, 0.976

The model includes fixed effects for period and treatment (AS MDI vs Proventil), and a random intercept.
[a] Relative potency is calculated as exp((a2-a1)/b) with bias-corrected accelerated bootstrap confidence interval.

Notes to the Programmer: The C_{15min} values for albuterol after each cumulative dose will be analyzed with a power law model. Natural log-transformed C_{15min} will be regressed onto the natural log transformed cumulative dose levels. The model will include fixed effects for period and treatment (AS MDI vs Proventil), and a random intercept. A test for treatment-by-ln-cumulative dose interaction will be conducted. If found to be non-significant at the 5% level, the interaction term will be dropped from the model, parallel slopes will be assumed, and the relative potency of AS MDI vs Proventil will be assessed (Finney, 1978; Table 2.18). If the linear or parallel line assumptions required for the Finney method appear to be violated, then an E_{max} model will be used to estimate relative potency. The bias-corrected and accelerated bootstrap will be used for either the Finney or Emax method to construct 90% CIs. While not a true assessment of dose proportionality, the proportionality of albuterol C_{15min} after cumulative dose administration (cumulative doses of 90, 180, 360, 720, and 1440 µg) will be assessed using the above power law model with separate slopes.

If an Emax model is needed, please replace the table above, replacing 'Finney' in the title with 'Emax', replace 'Intercept Estimate' in the column header with 'ED50', replace '(a1)' and 'a2' with '(e1)' and '(e2)'; replace the model footnote, and use this footnote for footnote [a]:
[a] Relative potency is calculated as (e1/e2) with bias-corrected accelerated bootstrap confidence interval.

Figure 2.14 C_{15min} Geometric Mean and Individual Values: Cumulative Dose-Concentration Profiles for Albuterol
Analysis Set: PK Analysis Set



Source: Table 2.14
Notes to Programmer:
The plot is for ln (concentration) by ln (cumulative dose), but show the back-transformed value on the x and y axis tick marks of the plot.
There should be two lines; one for AS MDI and one for Proventil that represent the separate slopes from the power law model. Also, in a text box, include the slope estimates and the 90% confidence intervals for each of the treatments.
Do not back-transform the slope. Also, plot the individual subject values for each treatment.
Remove the SE bars. Instead plot the individual values at each dose.
But if an Emax model is used instead of Finney method, please plot using log(response) and dose instead (not log(dose)). Do not show slope estimates and 90% CIs.

3. Safety

Adverse Events

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

	AS MDI (N=xxx)	Proventil (N=xxx)	Any Treatment (N=xxx)
	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]
Subjects With Serious TEAEs	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]
Subjects With Serious TEAEs Related to Study Treatment [b]	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]
Deaths - All Causes	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 3.1.2 Overall Summary of Treatment-Emergent Adverse Events Including Adverse Events During the Washout or Follow-up Periods
Analysis Set: Safety Analysis Set

	AS MDI (N=xxx)	Proventil (N=xxx)	Any Treatment (N=xxx)
	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]
Subjects With Serious TEAEs	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]
Subjects With Serious TEAEs Related to Study Treatment [b]	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]
Deaths - All Causes	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	AS MDI (N=xxx) n (%) [Events]	Proventil (N=xxx) n (%) [Events]	Any Treatment (N=xxx) n (%) [Events]
At Least One TEAE [a]	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]
Preferred Term 1	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]
System Organ Class 2	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]
Preferred Term 2	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.
If there are 0 AE's in the table, change cutpoint to 4%, 3%, or 2%. (2%, 3%, and 4% will likely yield the same table which would be same as a table requirement 2 or more subjects per preferred term).

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)	Primary System Organ Class	AE Verbatim (Preferred Term)	Treat. Emerg.	Event Serious	Onset Date (Study Day) [a]	Duration of Event	Severity	Relation -ship	Action	AE Treated	Outcome (Death)	Study Day Resolved/ Death
Treatment: AS MDI or Proventil												
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	Resolved (Yes)	P3
	…	…										

[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 first dose in the Period + 1. Tx = Period. Tx_y = Period and Day within Period. Pxx = Days after last dose in Period.

Report generated by program: PT007002/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.	Onset Day [b] (Day of Most Recent Dose)	Duration of Event [b]	Severity/ Relation-ship	Action/ (Outcome) (AE Treated)	Study Day Resolved [a]
Treatment: AS MDI or Proventil										
Center # (Investigator): Center ### (xxxxxxxxxx)										
xxxxxx	70/F/W	xxxx xxx xx xxxx	xxx xxx xxxxx xxxxxxx (xxxxxxxxxxxxxxxxxx)	Hospitalization / prolongation of existing Hospitalization (T1_Day 5-Day 8)	Yes	5 (T2_P1)	4	Moderate / Not Related	None (Recovered/Resolved) (Yes) Interrupted, Date Stopped: YYYY-12-07; AE abated: Yes; Date restarted: YYYY_12_08: AE reoccur? Yes	8

[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 first dose in the Period + 1. Tx = Period. Tx_y = Period and Day within Period. Pxx = Days after last dose in Period.
[b] Duration of event = Stop Day - Onset Day + 1.

Report generated by program: PT007002/sasdir/programs/statout/t030701.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 or Proventil							
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 Interrupted (Stopped: YYYY-MM-DD SAE Abated: Yes/No Treatment Restarted: YYYY-MM-DD SAE Reoccur: Yes/no) Permanently Discontinued (YYYY-MM-DD)	Moderate / Possibly / (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 – AS MDI
Analysis Set: Safety Analysis Set

Primary System Organ Class Preferred Term	AS MDI (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.

Report generated by program: PT007002/sasdir/programs/statout/t030901.sas Version YYYY-MM-DD xx:xx (Page n of N)

Table 3.9.2 TEAEs by Primary System Organ Class, Preferred Term, and Highest Severity – Proventil
Analysis Set: Safety Analysis Set

Table 3.10 Listing of Deaths
Analysis Set: All Subjects Screened

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

Treatment: A = AS MDI, B = Proventil, - = Not Treated.
TRT = Treatment.
[a] Days since Last Dose = Date of death - Date of last dose of study treatment + 1.

Report generated by program: PT007002/sasdir/programs/statout/t0310.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.

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

Subject ID (Treatment Sequence)	Age (yrs)[a]/ Gender (Race/Ethnicity)	Height(cm)/ Weight (kg)/ BMI (kg/m^2)	Randomized? (Study Day) [b]	Subject Study Status (Date of Last Dose [Study Day)} (Follow-up Call? Date) Date of Death [c]
Center # (Investigator): Center ### (xxxxxxxxxx)				
Xxxxxx (A/B)	Xx/M (x/xx)	xxx.x/ xx.x/ xx.x	Yes/No (xx)	Completed Study (YYYY-MM-DD [xxx]) (Yes YYYY-DD-MM) NA
Xxxxxx (A/-)	Xx/M (x/xx)	xxx.x/ xx.x/ xx.x	Yes/No (xx)	Discontinued Investigator's Decision (YYYY-MM-DD [xxx]) (No)
Xxxxxx (B/A)	Xx/M (x/xx)	xxx.x/ xx.x/ xx.x	Yes/No (xx)	Discontinued Subject Lost to Follow up (YYYY-MM-DD [xxx]) (No)
Xxxxxx (B/-)	Xx/M (x/xx)	xxx.x/ xx.x/ xx.x	No (NA)	Discontinued Investigator's Decision (YYYY-MM-DD [xxx]) (No)
Xxxxxx (A/B)	Xx/M (x/xx)	xxx.x/ xx.x/ xx.x	No (NA)	Discontinued Adverse Event (YYYY-MM-DD [xxx]) (No) Death: YYYY-MM-DD

Treatment: A = AS MDI, B = Proventil, - = 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.
[a] Age = integer part of ((Visit 1 date – Birth date +1)/365.25)
[b] 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.
[c] Study Day is date of date of the last dose of study drug - date of first dose of study drug + 1.

Source: xxxxxxx.sas7bdat

Report generated by program: PT007002/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/Discontinuation/Discontinuation 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 (Time of First Dose – Time of Last Cumulative Dose)/ Washout Length (days) [a]	Period 2 Treatment (Time of First Dose – Time of Last Cumulative Dose)/ Washout Length (days) [a]
Study Center # / (Investigator): ### / (xxxxxxxxxx)			
xxxxx	A/B (A/B)	AS MDI (hh:mm - hh:mm)/ (7)	Proventil (hh:mm - hh:mm)/ (7)
xxxxx	B/A (B/A)	Proventil (hh:mm - hh:mm)/ (7)	AS MDI (hh:mm - hh:mm)/ (7)
xxxxx	A/B (A/-)	AS MDI (hh:mm - hh:mm)/ (7)	

Treatment: A = AS MDI, B = Proventil, - = Not Treated.
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 = (date of subsequent treatment (or follow-up telephone call) - date of previous study treatment - 1).

Source: xxxxxxx.sas7bdat

Report generated by program: PT007002/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	xxxxxxxxxxxxxx (Inclusion Criterion #n)
xxxxxx	YYYY-MM-DD	xx	Female	W	xxxxxxxxxxxxx (Inclusion Criterion #n)
xxxxxx	YYYY-MM-DD	xx	Male	W	xxxxxxxxxxxxx (Inclusion Criterion #n)
xxxxxx	YYYY-MM-DD	xx	Male	W	xxxxxxxxxxxxx (Inclusion Criterion #n)
Xxxxxx	YYYY-MM-DD	Xx	Female	W	<Reason for discontinuation from the Discontinuation/Completion CRF>

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: PT007002/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.

4.2 Protocol Deviations

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

Subject ID	Treatment Sequence	Age (yrs)/ Gender Race [a]	Informed Consent Signed	Informed Consent Study Day [a]	Eligibility				
					Visit	Study Day [a]	Inclusion/ Exclusion Criteria Satisfied	Type of Failed Criteria	Failed Criteria Number
Center # (Investigator): Center ### (xxxxxxxxxx)									
xxxxxx	A/B	xx/F/W	Yes	-xx	Visit 1	-xx	No	Inclusion	6

Treatment: A = AS MDI, B = Proventil, - = 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.
[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: PT007002/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 Actual Treatment, 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

						Pre-Dose		Post-Dose		
Subject ID	Treatment Sequence	Age (yrs) /Gender/ Race [a]	Visit	Effort Date	Time of Ventolin HFA Dose (24 h clock)	FEV_1 (L)	FVC (L)	FEV_1 (L)	FVC (L)	Reversibility % (Did subject withhold asthma maintenance medications and/or SABA within previous 6 hours?)
Center # (Investigator): Center ### (xxxxxxxxxx)										
xxxxx	A/B	70/F/W	1	YYYY-MM-DD	xx:xx	x.xxx	x.xxx	x.xxx	x.xxx	
			1a	YYYY-MM-DD	xx:xx	x.xxx	x.xxx	x.xxx	x.xxx	xx.x (Yes)
			1b	YYYY-MM-DD		x.xxx	x.xxx	x.xxx	x.xxx	xx.x (Yes)
xxxxx	B/A	70/F/W	1	YYYY-MM-DD	xx:xx	x.xxx	x.xxx	x.xxx	x.xxx	xx.x (Yes)
xxxxx	A/B	70/F/W	1	YYYY-MM-DD		x.xxx	x.xxx	x.xxx	x.xxx	xx.x (Yes)

Treatment: A = AS MDI, B = Proventil, - = 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.
NA = not applicable.

Source: xxxxxxx.sas7bdat

Report generated by program: PT007002/sasdir/programs/statout/l03.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer: Sort by Treatment Sequence, 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

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

Treatment: A = AS MDI, B = Proventil, - = 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.
[a] Missing month of Date Asthma First Diagnosed will be 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: PT007002/sasdir/programs/statout/l0401.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer: Sort by Treatment Sequence, 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	System Organ Class	Diagnosis or Surgery/ (Preferred Term)	Onset Date (Year/ Month)	Onset Day [a]	Still Present?	End Date (Year/ Month)	End Day [b]
Center # (Investigator): Center ### (xxxxxxxxxx)									
xxxxxx	A/B	70/F/W		xxxxx/(xxxx)	YYYY-MM	-xxx	No	YYYY-MM	xxx
			xxxxxxxx						
				xxxxx/(xxxx)	YYYY-MM	-xxx	No	YYYY-MM	xxx
			xxxxxx						
xxxxxx	B/A	70/F/W		xxxxx/(xxxx)	YYYY-MM	-xxx	No	YYYY-MM	xxx
			xxxxxxxxxxxxxxxx						
				xxxxx/(xxxx)	YYYY-MM	-xxx	Yes		Ongoing
			xxxxxxxxxx						
xxxxxx	A/B	70/F/W		xxxxx/(xxxx)	YYYY-MM	-xx	No	YYYY-MM	xxx
			xxxxxxxxxxxx						
xxxxxx	B/A	70/F/W		xxxxx/(xxxx)	YYYY-MM	-xxx	No	YYYY-MM	xxx
			xxxxxxxxxx						

Treatment: A = AS MDI, B = Proventil, - = Not Treated.
[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: PT007002/sasdir/programs/statout/l0402.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer: Sort by Treatment Sequence, 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 – WOCBP Only

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 [a]	Result
Center # (Investigator): Center ### (xxxxxxxxxx)									
xxxxxx	A/B	70/F/W	Woman of Non-Childbearing Potential (Non-WOCBP)		Visit 1	YYYY-MM-DD	Not Done	NA	NA
xxxxxx	B/A	70/F/W	Woman of Childbearing Potential (WOCBP)	Yes	Visit 2	YYYY-MM-DD	Serum Pregnancy Test	xxx	Positive

Treatment: A = AS MDI, B = Proventil, - = Not Treated.
[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: PT007002/sasdir/programs/statout/l0403.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer:
Sort by Treatment Sequence, Center, Investigator, Subject ID within Center, Visit, and Study Day of Pregnancy Test.
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)	xxxxxxxxxxxx (xxxxxx) (xxxxxx)	90/ MCG/ IH/ PRN	# xxx	2008-XX-XX		Yes		-22		Yes/Yes/No
			Other, <specify>	2008-XX-XX		Yes		-22		Yes/Yes/No

Treatment: A = AS MDI, B = Proventil, - = 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 last dose.

Sources: xxxxxxx.sas7bdat

Report generated by program: PT007002/sasdir/programs/statout/l0404.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer:
Sort by Treatment Sequence, 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-IP Medication at Onset of SAE	Dose/ Unit/ Route/ Frequency	Started Treatment/ Most Recent IP/Date of Most Recent IP/ Treatment at Onset of AE/Non-IP 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)	Xxxxxxxxxx/ Xxxxxxxxx/ YYYY-MM-DD	Ventolin HFA	90/µg/ IH/PRN	Yes/B/ YYYY-MM-DD/ Yes/Yes	2008-XX-XX	Yes		-22	Yes / Yes (Pre-existing /Underlying disease or Prior or Concomitant Medication
xxxx (B/A)	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 or Other

Treatment: A = AS MDI, B = Proventil, - = Not Treated.
IP = Investigational Product.
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 first dose in the Period + 1. Tx_y = Treatment Period and Day within Treatment Pxx = Days after last dose in period.

Sources: xxxxx.sas7bdat
Report generated by program: PT007002/sasdir/programs/statout/l0405.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 and Compliance

Listing 5.1.1 Study Drug Administration
Analysis Set: All Subjects Randomized

Subject ID	Treatment Sequence	Visit (Study Day [a])	Dose Sequence	Date and Time of On-Site Study Dose (Study Day [a])	Study Medication Component ID	Number of Puffs Taken
Study Center # / (Investigator): ### (xxxxxxxxxx)						
xxxxxx	A/-	Visit x (Tx_y)	Dose 1	YYYY-MM-DD (hh:mm) (Tx_y)	Bxxxxx	x
		Visit x (Tx_y)	Dose 2	YYYY-MM-DD (hh:mm) (Tx_y)	Bxxxxx	x

Treatment: A = AS MDI, B = Proventil, - = Not Treated.
[a] Study Day is Date - Date of first dose in the Period + 1. Tx = Period. Tx_y = Period and Day within Period. Pxx=Days after last dose in the Period.

Source: xxxxxxx.sas7bdat

Report generated by program: PT007002/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, Atrovent, and Pulmicort Flexhaler Dispensing
Analysis Set: All Subjects Randomized

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

Treatment: A = AS MDI, B = Proventil, - = Not Treated.
[a] Study Day is Date – Date of first 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: PT007002/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 Overall and by Dose
Analysis Set: All Subjects Randomized

Subject ID (Treatment Sequence)	Age (yrs)/ Gender/ Race	Treatment Period	Dose	Number of Puffs Taken	Expected [a]	Dose Level % of Expected Exposure (%) [b]	Taken Overall	Overall % of Expected Exposure (%) [c]
Center # / (Investigator): ### (xxxxxxxxxx)								
1001 (A/B)	70/F/W	1	Dose 1	1	1	100.00	xx	93.75
	70/F/W		Dose 2	1	1	xx.xx		
	70/F/W		Dose 3	x	2	xx.xx		
	70/F/W		Dose 4	x	4	xx.xx		
	70/F/W		Dose 5	x	8	xx.xx		
	70/F/W							
	70/F/W	2	Dose 1	1	1	100.00	xx	xx.xx
	70/F/W		Dose 2	1	1	xx.xx		
	70/F/W		Dose 3	x	2	xx.xx		
	70/F/W		Etc...					

Treatment: A = AS MDI, B = Proventil, - = Not Treated.
[a] The total expected number of puffs for a treatment day was 16 puffs.
[b] Dose Level % of Expected Exposure = Total number of puffs of a treatment taken for a dose level/total expected puffs of a treatment taken for the dose level, multiplied by 100.
[c] Overall % of Expected Exposure = Total number of puffs of a treatment taken on a study day/total expected puffs of a treatment taken on the study day (16 puffs), multiplied by 100.

Source: xxxxxxx.sas7bdat
Report generated by program: PT007002/sasdir/programs/statout/l0502.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer:
Sort by Center, Subject within Center, Treatment Period, and Treatment 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. .

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

Subject ID	Treatment Sequence	Age (yrs)/ Gender/ Race	Treatment/Visit	Effort Date	-60 Minute Pre-Dose Effort Time (24 h clock)	Prior to Study Visit, Subject has: Not Had Xanthine Containing Products for at Least 6 Hours	Prior to Study Visit, Subject has: Withheld Asthma Medications Including Corticosteroids for at Least 8 Hours
Center # (Investigator): Center ### (xxxxxxxxxx)							
xxxxxx	A/B	70/F/W	A/Visit 2	YYYY-MM-DD	8:14:57	No	No
			B/Visit 3	YYYY-MM-DD	8:14:57	No	No

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

Source: xxxxxxx.sas7bdat

Report generated by program: PT007002/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.
If Race is 'O' (other), concatenate it with the specified race. 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)	AS MDI	Visit 2	YYYY-MM-DD
		Visit 3	YYYY-MM-DD
Xxxxxx (B/-)	Proventil	Visit 2	YYYY-MM-DD

Treatment: A = AS MDI, B = Proventil, - = Not Treated.

Source: xxxxxxx.sas7bdat

Report generated by program: PT007002/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)	Visit Missed	Treatment	Missed Due to Asthma Related Issues
Study Center # / (Investigator): ### (xxxxxxxxxx)			
Xxxxxx (A/B)	Visit xx	AS MDI	Yes
Xxxxxx (B/-)	Visit xx	Proventil	No
	Visit xx		Unknown

Treatment: A = AS MDI, B = Proventil, - = Not Treated.

Source: xxxxxxx.sas7bdat

Report generated by program: PT007002/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 Medication 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)	FVC (L)	FEV_1/ FVC(%)	FEF 25-75 (L/sec)
Center # (Investigator): Center ### (xxxxxxxxxx)										
Xxxxxx (A/B)	53/F/W/xx x	Visit 1		YYYY-MM-DD (-xx)	Yes (xx:xx AM/PM)	-60 Min Pre-Dose (xx:xx)	x.xxx [x.xxx] (xx.x%) (x)	x.xxx [x.xxx] (xx.x%) (x)	xx.x	x.xxx [x.xxx] (xx.x%)
		Repeat for Visit 1a or 1b, as necessary.		YYYY-MM-DD (xx)	Yes (xxxxxx)	15 Min Dose 1 (xx:xx)	x.xxx (xx.x%) (x)	x.xxx (xx.x%) (x)	xx.x	x.xxx (xx.x%)
		Visit 2	A/YYYY-MM-DD hh:mm	YYYY-MM-DD (xx)	Yes (xxxxxx)	15 Min Dose 1 (xx:xx)	x.xxx (xx.x%) (x)	x.xxx (xx.x%) (x)	xx.x	x.xxx (xx.x%)
		Repeat for Visit 3 or Unscheduled, as necessary.								

Treatment: A = AS MDI, B = Proventil, - = Not Treated.
NA = Not applicable.
[a] Study Day is Date – Date of first dose in the Period + 1. Tx = Period. Tx_y = Period and Day within Period. Pxx = Days after last dose in Period.
[b] Grade is coded: 1=Acceptable 2=Borderline Acceptable 3=Unacceptable.

Source: xxxxxxx.sas7bdat
Report generated by program: PT007002/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.

4.6.2 Pharmacokinetics

Listing 6.5 Plasma Concentrations of Albuterol by Subject ID, Treatment, and Timepoint
Analysis Set: Safety Analysis Set

Subject ID (Treatment Sequence)	Treatment	Treatment Period	Date of Sample/ Dose Number	Time Pre/Post-Dose (minutes) [a]	Scheduled Sample Time Relative to Dose (24 Hour clock)	Actual Sample Time Relative to Dose (24 Hour clock)	Time Deviation (Hours)	Plasma Concentration
								Albuterol (pg/mL)
Study Center # / (Investigator): ### / (xxxxxxxxxx)								
xxxxxx (A/B)	A	1	Yyyymmdd/ Dose 5	-30 Pre	hh:mm	hh:mm	x.xx	xx.x*
				+15 Post				
				+30 Post				
				+60 Post				
				+120 Post				
				+180 Post				
				+240 Post				
				+300 Post				
				+360 Post				
				+480 Post				
				+600 Post				
				+720 Post				
			Etc….					
	B	2	Yyyymmdd/ Dose 1	-30 Pre	hh:mm	hh:mm	x.xx	NA
				+15 Post				
			Etc…					

Treatment: A = AS MDI, B = Proventil.
Lower limit of quantification is 50 pg/mL.
BLQ = Below the limit of quantification.
NA = not available.
[a] Nominal timepoint.
*Excluded from summary statistics. Actual sampling time differs from scheduled sampling time by greater than the acceptable time deviation specified in the database edit check specifications.

Source: xxxx.sas7bdat
Report generated by program: PT007002/sasdir/programs/statout/l0605.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer: If the serum concentration is missing, populate empty columns with 'NA'. Sort by Center, Subject ID within Center, Treatment, Date, and Nominal Timepoint.

Listing 6.6 Derived Pharmacokinetic Parameters of Albuterol by Subject ID and Treatment Period
Analysis Set: PK Analysis Set

Subject ID (Treatment Sequence)	Age	Gender	Race	Treatment Period	Treatment	PK Parameter	Result
Center # / (Investigator): ### / (xxxxxxxxxx)							
Xxxxxx (A/B)	xx	x	xxxx	1	A	AUC_{0-t} (pg/mL)	xx.x
						C_{max} (pg/mL)	xx.x
						C_{15min} (pg/mL)	xx.x
						t_{max} (min)	xx.x
				2	B	Etc.	NA
							NA

Treatment: A = AS MDI, B = Proventil.
NA = not available. NE = not estimable.

Source: xxxx.sas7bdat
Report generated by program: PT007002/sasdir/programs/statout/l0606.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer: If the PK parameter result is missing, populate empty columns with 'NA'.
Sort by Center, Subject ID within Center, Treatment Period, and PK Parameter.

4.7 Adverse Event Listings

Listing 7.1 Adverse Events by Primary System Organ Class, Preferred Term, Treatment, 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? [c]	Onset Day [a]	Duration of Event [b]	Severity / Relationship	Action (Outcome) (AE Treated)	Study Day Resolved /Death[a]
xxxxxxxxxxxxxxxx	xxxxxxxxxx xxxxxx	xxxxxxxxx ### (xxxxxxxxxx)	Xxxxxx (A/B)	70/F/W	Yes / No	T1_P1	xx	Moderate / Yes	None(Recovered/Resolved) (Yes)	Tx_P5
				70/F/W	Yes / No	T2_P2	xx	Moderate/ Yes	Drug Interrupted(Recovering/Resolving)g (Yes)	
	xxxxxxxxxx xxxxxx	xxxxxxxxx ### (xxxxxxxxxx)	Xxxxxx (A/B)	70/F/W	Yes / Yes	T1_P1	xx	xxxxxxxx/ xxxxxxxxx	Dose not changed (Recovered/Resolved with sequelae)(No)	T2_P7
		xxxxxxxx ### (xxxxxxxxxx)	Xxxxxx (A/B)	70/F/W	Yes / No	T2_P2	xx	xxxxxxxx/ xxxxxxxxx	Dose not changed (Recovered/Resolved with sequelae)(No)	
…										
xxxxxxxxxxxxxxxxxx xxxx	xxxxxxxxxx xxxxxx	xxxxxxxxxx ### (xxxxxxxxxx)	Xxxxxx (A/B)	70/F/W	# /No		xx	xxxxxxxx/ xxxxxxxxx	Dose not changed (Recovered/Resolved with sequelae)(Yes)	
			Xxxxxx (A/B)	70/F/W	Yes / Yes	T2_P2	xx	xxxxxxxx/ xxxxxxxxx	Drug withdrawn (Recovering/Resolving) (Yes)	

Treatment: A = AS MDI, B = Proventil, - = Not Treated.
[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 first dose in the Period + 1. Tx = Period. Tx_y = Period and Day within Period. Pxx = Days after last dose in 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] Duration of Event = Stop Day - Onset Day + 1.
[c] # indicates that it could not be determined whether the AE had onset during study treatment.

Source: xxxx.sas7bdat

Report generated by program: PT007002/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	xxxxxxxxxxxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
	xxxxxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
		xxxxxxxxxxxxx
xxxxxx	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxxxxxxxx
		xxxxxxxxxx
	xxxxxxxxxxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
xxxxxxxxxxxxxx	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxxxxxxxxxx
		xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx

MedDRA Version 21.0 was used for coding.

Source: xxxxxxx.sas7bdat

Report generated by program: PT007002/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/ Onset Day/ Occurred on or After Start of Treatment on Day 1 [a]	Primary System Organ Class	AE Verbatim (Preferred Term)	Treat. Emerg. [b]	Event Serious	Duration of Event	Severity	Relation-ship	Action	AE Treated ?	Outcome (Death?)	Day Resolved/ Death [a]
Treatment: AS MDI													
Center # (Investigator): Center ### (xxxxxxxxxx)													
xxxxx (A/B)	70/F/W	YYY-MM-DD/ T1_1/Yes	xxx xxx xxxxx	AE 1 (xxxxxxxxxxxx)	Yes	No	xx	Moderate	No	Dose not changed	No	Recovering/Resolving	
		YYY-MM-DD/ T1_P1/ NA	xxx xxx xxxx	AE 2 (xxxxxxxxxx)	No	No	xx	Moderate	Yes	Drug Interrupted	Yes	Not Recovered/Not Resolved (Yes)	T1_P3
		…		…									

Treatment: A = AS MDI, B = Proventil, - = Not Treated.
[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 first dose in the Period + 1. Tx = Period. Tx_y = Period and Day within Period. Pxx = Days after last dose in 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.

Sources: adae.sas7bdat

Report generated by program: PT007002/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 ID)	Lab Parameter (Unit)	Assay Value	Reference Range Low-High	Flag [b]
Center # (Investigator): Center ### (xxxxxxxxxx)									
xxxxxx (A/B)	70/F/W	Screening Visit 1 (-xx)	YYYY-MM-DD (-xx)	Pre-dose (hh:mm)	xxxxxx	xxxxxxxxx x	xxx	xxx-xxx	L/H

Treatment: A = AS MDI, B = Proventil, - = Not Treated.
NA = Not Applicable.
[a] A negative number for study day denotes the number of days prior to the start of study treatment.
[b] N = Normal; L = Low; H = High; Abn. = Abnormal; I=Indeterminate;

Source: adlb.sas7bdat

Report generated by program: PT007002/sasdir/programs/statout/l0801.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer:
Sort by Treatment Sequence, Center, Subject ID, Date of Visit, Nominal Time of Collection, and Lab Parameter. In footnote [b], delete 'I=Indeterminate' if this flag does not exist in the data. Delete '(LAB ID)' if this does not exist in the data.
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

Subject ID (Treatment Sequence)	Age (yrs)/ Gender/ Race	Visit (Study Day [a])	Treatment Time (24 h clock) Collection Date (Study Day) [a]	Nominal Time of Collection (24 hr clock)	Lab Name (LAB ID)	Lab Parameter (Unit)	Assay Value	Reference Range Low-High	Flag [b]	Change From Baseline [c]
Country Center # (Investigator): xxxxxxxxxxxxxxxxxx Center ### (xxxxxxxxxx)										
xxxxxx (A/B)	70/F/W	Screening Visit 1a (-xx)	10:13 YYYY-MM-DD (1)	Pre-dose (hh:mm)	xxxxxx	xxxxxxxxxx	xxx	xxx-xxx	L/H	x.xxx

Treatment: A = AS MDI, B = Proventil, - = Not Treated.
NA = Not Applicable.
[a] A negative number for study day denotes the number of days prior to the start of study treatment.
[b] N = Normal; L = Low; H = High; Abn. = Abnormal; I=Indeterminate; Albuterol has known pharmacodynamic effects on glucose and potassium. As such, the standard reference ranges for glucose and potassium are not applicable post administration of albuterol.

[c] For change from baseline, baseline is defined as the last available pre-dose measurement taken prior to the start of treatment on Day 1 of the treatment period.

Source: adlb.sas7bdat

Report generated by program: PT007002/sasdir/programs/statout/l0802.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. In footnote [b], delete 'I=Indeterminate' if this flag does not exist in the data. Delete '(LAB ID)' if this does not exist in the data.
For the post-dose glucose and potassium Reference Range, put "N/A".
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 8.3 Laboratory Test Comments
Analysis Set: All Subjects Randomized

Subject ID (Treatment Sequence)	Visit (Study Day [a])	Time of Treatment (24 hr clock))	Collection Date (Study Day [a])	Nominal (Actual) 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)	Visit 2 (T1_1)	hh:mm	YYYY-MM-DD (T1_1)	-60 Min Pre-Dose (hh:mm)	LabCorp	Chemistry	Glucose (mmol/L)	xx	xx-xx	L	xxxxxx

Treatment: A = AS MDI, B = Proventil, - = Not Treated.
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 first dose in the Period + 1. Tx = Period. Tx_y = Period and Day within Period. Pxx = Days after last dose in Period.
[b] N = Normal; L = Low; H = High; Abn. = Abnormal; I=Indeterminate;

Source: adlb.sas7bdat

Report generated by program: PT007002/sasdir/programs/statout/l0803.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer:
Sort by Treatment Sequence, 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 (Actual Time) of Assessment (24 h clock)	Systolic BP (Change from baseline) [b] (mmHg)	Diastolic BP (Change from baseline) [b] (mmHg)	Height (cm)	Weight (kg)	BMI (kg/m^2)
Center # (Investigator): Center ### (xxxxxxxxxx)									
Xxxxxx (A/B)	70/F/W	Screening Visit 1 YYYY-MM-DD (-xx)	NA	NA (NA)	xxx	xxx	xxx	xxx.x	xxx.x
		Screening Visit 1a YYYY-MM-DD (-xx)	NA	NA (NA)	xxx	xxx	xxx	xxx.x	xxx.x
		Visit 2 YYYY-MM-DD (Tx_y)	hh:mm	-60 Min.Pre-Dose (xx:xx)	xxx	xxx	xxx	xxx.x	xxx.x
				+15 Min. Post-Dose 1 (xx:xx) (xx)	xxx	xxx			
				+15 Min. Post-Dose 2 (xx:xx) (xx)	xxx (xx)	xxx (xx)			
		Repeat for Visit 3 and Unscheduled as necessary.							

Treatment: A = AS MDI, B = Proventil, - = Not Treated.
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 first dose in the Period + 1. Tx = Period. Tx_y = Period and Day within Period. Pxx = Days after last dose in Period.
[b] For change from baseline, baseline is defined as the last available pre-dose measurement taken on Day 1 of the treatment period prior to the start of dosing of the treatment period.

Source: advs.sas7bdat

Report generated by program: PT007002/sasdir/programs/statout/l0901.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer:
Sort by Treatment Sequence, Center, Subject ID, Date of Visit, and Nominal Time of Assessment.
Nominal time of assessment is the SAP-specified derived time window.
Show Nominal Window of 'Pre-Dose' from dataset as "Pre-Dose 60 Min." here in this listing as indicated above.
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 (Actual Time) of Assessment (24 h clock)	Heart Rate (Change) (BPM)	Interval Raw Value (Change From Baseline) [b] RR (ms)	PR (ns)	QRS Axis (degrees)	QRS (ms)	QT (ms)	QTcF (ms)	Any Clinically Significant Abnormalities on a Study Day? [c]
Center # (Investigator): Center ### (xxxxxxxxxx)												
xxxxx (A/B)	70/F/W	Visit 1 YYYY-MM-DD (-xx)	NA	NA (NA)	xx.x	xxx	xxx	xx	xxx	xxx	xx	No
		Visit 1a or 1b, as necessary YYYY-MM-DD (-xx)	NA	NA (NA)	xx.x	xxx	xxx	xx	xxx	xxx	xx	No
		Visit 2 YYYY-MM-DD (Tx_y)	Hh:mm	60 Min. Pre-Dose (xx:xx)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	No
				15 Min. Post-Dose (xx:xx)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	Yes
		Repeat for Visit 3 and Unscheduled	NA									

Treatment: A = AS MDI, B = Proventil, - = Not Treated.
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.
[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 first dose in the Period + 1. Tx = Period. Tx_y = Period and Day within Period. Pxx = Days after last dose in Period.
[b] For change from baseline, baseline is defined as the last available pre-dose measurement taken on Day 1 of the treatment period prior to the start of dosing.

Source: eg.sas7bdat

Report generated by program: PT007002/sasdir/programs/statout/l0902.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer: Sort by Treatment Sequence, Center, Subject ID, Date of Visit, and Nominal Time of Assessment.
Nominal time of assessment is the SAP-specified derived time window.
Show Nominal Window of 'Pre-Dose' from dataset as "Pre-Dose 60 Min." here in this listing as indicated above.
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	Study Day [a]	Comment Applies To:	Comments
Study Center # / (Investigator): ### (xxxxxxxxxx)						
xxxxx	A/B	70/F/W	Screening Visit 1	Tx_y	Subject	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
			Screening Visit 1a		Eligibility	xxxxxxxxxxx
			Screening Visit 1b		Study Medication	
			Visit 2 Treatment 1		Adverse Event	
			Day 1		Blood Pressure	
			Visit 3 Treatment 1		12-Lead ECG	
			Day 1		Laboratory Test	
			…		Spirometry	
					Visit Scheduling	
			Premature		PK Sampling	
			Discontinuation		Other:	
			Telephone		xxxxxxxxxxxxxx	
			Follow-up			
			Unscheduled			

Treatment: A = AS MDI, B = Proventil, - = Not Treated.
[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 first 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: PT007002/sasdir/programs/statout/l0903.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.

5. CLINICALTRIALS.GOV: DISPOSITION TABLES

Table 1.1 Subject Disposition
Analysis Set: All Subjects Randomized

	Treatment Sequence	
	AS MDI/ Proventil (N=xxx)	Proventil/ AS MDI (N=xxx)
	n (%)	n (%)
Started (Randomized)	xx (100.0)	XX (100.0)
Not Treated	xx (xx.x)	xx (xx.x)
Treated in at least one period		
Treated in 1 Period Only	xx (xx.x)	xx (xx.x)
Treated in 2 Periods	xx (xx.x)	xx (xx.x)
Completed Treatment <Programmer this is from the End of Treatment/Discontinuation CRF>	xx (xx.x)	xx (xx.x)
Premature TreatmentDiscontinuation	xx (xx.x)	xx (xx.x)
Reason for Premature Discontinuation		
Administrative Reasons	xx (xx.x)	xx (xx.x)
Adverse Event	xx (xx.x)	xx (xx.x)
Lack of Efficacy	xx (xx.x)	xx (xx.x)
Subject Discretion - Withdrawal of Consent	xx (xx.x)	xx (xx.x)
Subject Discretion - Asthma	xx (xx.x)	xx (xx.x)
Subject Discretion - Other	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)
Subject Lost-to-Follow-up	xx (xx.x)	xx (xx.x)
Major Protocol Deviation	xx (xx.x)	xx (xx.x)
Protocol-Specified Discontinuation Criteria	xx (xx.x)	xx (xx.x)
FEV_1 Stability Criteria Sec 5.1.4	xx (xx.x)	xx (xx.x)
Requirement OF any Prohibited Medications Listed in Sec 7.7.3	xx (xx.x)	xx (xx.x)
Positive Pregnancy Test	xx (xx.x)	xx (xx.x)
Asthma Worsening Requiring Change in Asthma Treatment Sec 3.9	xx (xx.x)	xx (xx.x)
Treatment Code Broken by Investigator	xx (xx.x)	xx (xx.x)
Other	xx (xx.x)	xx (xx.x)

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. Percentages are percentages of all subjects randomized.

Table 1.2 Subject Disposition: Period 1
Analysis Set: All Subjects Randomized

Notes to Programmer: Replace column header of 'Treatment Sequence" in Table 1.1 with "Treatment" and the 2 Treatment Sequences with the 2 Treatments in Period 1. Percentages are percentages of all subjects randomized.

Table 1.3 Subject Disposition: Washout Between Period 1 and Period 2
Analysis Set: All Subjects Randomized Who Entered the Washout

Notes to Programmer: Replace column header of 'Treatment Sequence" in Table 1.1 with "Treatment in Period 1" and the 2 Treatment Sequences with the 2 Treatments in Period 1. Instead of 'Started (Randomized)' in Table 1.1 use 'Started (Randomized, Completed Period 1 Test Day, and Entered the Washout Period)'. Note that subject who entered the washout can be determined from the dates of Period 1 treatment date and the Visit 2 and Visit 3 sometimes, and the subject LTF date from the End of Treatment/Discontinuation eCRF. If a subject did not go to Period 2, and dropped during the washout, the only subjects we can count are those LTF and have an LTF date on the End of Treatment/Discontinuation eCRF.
The site will be asked to identify if a subject entered the Washout Period between Periods 1 and 2 when the subjects dropped prior to Period 2.

Table 1.4 Subject Disposition: Period 2
Analysis Set: All Subjects Randomized

Notes to Programmer: Replace column header of 'Treatment Sequence" in Table 1.1 with "Treatment in Period 2" and the 2 Treatment Sequences with the 2 Treatments in Period 2. Instead of 'Started (Randomized)' in Table 1.1 use 'Started (Randomized and Attended the Period 2 Test Day)'.